Nephrol Dial Transplant (2012) 27: 891–898
doi: 10.1093/ndt/gfs038

NDT
Nephrology Dialysis Transplantation

Editorial Review

Significance of hypo- and hypernatremia in chronic kidney disease

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Abstract
Both hypo- and hypernatremia are common conditions, especially in hospitalized patients and in patients with various comorbid conditions such as congestive heart failure or liver cirrhosis. Abnormal serum sodium levels have been associated with increased mortality in numerous observational studies. Patients with chronic kidney disease (CKD) represent a group with a high prevalence of comorbid conditions that could predispose to dysnatremias. In addition, the failing kidney is also characterized by a gradual development of hyposthenuria, and even isosthenuria, which results in further predisposition to the development of hypo- and hypernatremia in those with advancing stages of CKD. To date, there has been a paucity of population-wide assessments of the incidence and prevalence of dysnatremias, their clinical characteristics and the outcomes associated with them in patients with various stages of CKD. We review the physiology and pathophysiology of water homeostasis with special emphasis on changes occurring in CKD, the outcomes associated with abnormal serum sodium in patients with normal kidney function and the results of recent studies in patients with various stages of CKD, which indicate a substantial incidence and prevalence and significant adverse outcomes associated with dysnatremias in this patient population.

Keywords: chronic kidney disease; hypernatremia; hyponatremia; mortality; serum sodium

Introduction

Hyponatremia is one of the most common electrolyte abnormalities encountered in clinical practice, occurring in as many as 42% of acutely hospitalized patients [1]. Hyponatremia is associated with many different disease states such as congestive heart failure (CHF), liver cirrhosis, pneumonia and acquired immune deficiency syndrome, and is regarded as an important marker of the severity of these conditions [2, 3]. Other risk factors of hyponatremia are advanced age [1], male gender[1], low body weight [4, 5] and in nursing home populations also hypotonic fluid intake, low-sodium diet and tube feeding [6]. Both hypo- and hypernatremia are associated with significant increases in mortality in hospitalized patients and in patients with various comorbid conditions [7–28]. The development of vasopressin receptor antagonist medications that are able to induce a selective water diuresis without affecting sodium excretion [29] has led to renewed interest in the link between hyponatremia and various adverse outcomes. These medications have been shown to reliably correct hyponatremia [30–33], and hence could represent therapeutic options for patients under a variety of circumstances.

Chronic kidney disease (CKD) is known to affect the ability of the kidneys to regulate water homeostasis [34], and hence the risk of both hypo- and hypernatremia can increase with advancing stages of CKD. In spite of such physiological considerations, the results of earlier small observational studies suggested that frank hypo- or hypernatremia resulting from advancing CKD alone are rare or even non-existent even in patients with very advanced stages of non-dialysis-dependent CKD [35]. However, there has been a lack of population-level surveys of the incidence and/or prevalence of hypo- or hypernatremia in patients with CKD. It has also been unclear to what extent dysnatremias are associated with outcomes in patients with various stages of non-dialysis-dependent CKD. Due to their high numbers and their particular disease characteristics that predispose them to dysnatremias, patients with CKD represent a large and under-studied group in whom the characteristics and the consequences of both hypo- and hypernatremia still need to be clarified. In this review, we discuss briefly the physiology and pathophysiology of water homeostasis, the consequences of hypo- and hypernatremia in patients with normal kidney function and recent findings regarding the characteristics and outcomes associated with dysnatremias in patients with various stages of CKD.

Physiological background and significance of dysnatremias in patients with normal kidney function

Sodium is the most abundant electrolyte in the extracellular fluid, and it is the main contributor to extracellular tonicity

[36]. The physiological regulation of serum sodium level is maintained by balancing water intake and water excretion; the former through control of thirst sensation and the latter through control of antidiuretic hormone (ADH) secretion [36]. The ADH vasopressin (VP) [37] stimulates the plasma membrane accumulation of a water channel, aquaporin 2, which is a member of a family of water channel molecules that is located primarily in the kidney collecting duct principal cells [38]. The accumulation of aquaporin 2 in the collecting duct epithelium increases its water permeability, allowing osmotic equilibration of the luminal fluid with the surrounding interstitium and leading to urinary concentration [39].

Water balance can be disturbed by pathological states causing either abnormal water intake (through disordered thirst sensation or impeded access to water), changes in ADH secretion that override the primary osmotic stimulus for this hormone or abnormalities involving the VP receptor or aquaporin 2 in the collecting duct [40]. The resulting water excess or deficit leads to abnormal dilution or concentration of the extracellular fluid, most readily measured through concentration changes of serum sodium and hence resulting in hypo- or hypernatremia. As a result of such alterations in extracellular tonicity, a concentration gradient may occur between the intra- and extracellular space especially after rapidly developing hypo- or hypernatremia with water shifts leading to cellular swelling or shrinking. The physiological consequences of this are most acutely recognized in the central nervous system, where they could lead to potentially fatal brain edema or osmotic demyelination syndrome, respectively [41–43]. The impact of transcellular water shifts on the structure and function of organs whose cells are not limited to a closed space such as the cranium is less clear, but there have been suggestions that hyponatremia could be implicated in bone fractures [44–46], rhabdomyolysis [47], CHF and/or pulmonary edema [48, 49].

Based on these physiological considerations, it is plausible to postulate that both hypo- and hypernatremia can lead to adverse clinical consequences and potentially result in increased deaths, especially if they occur acutely. Outcomes associated with abnormal serum sodium levels have been explored by a substantial number of observational studies [7–28], mostly in the setting of acute hospitalization, or in patient populations known to be at risk for the development of abnormal serum sodium levels (such as patients with CHF or liver cirrhosis) (Table 1). The majority of these observational studies focused on the association of hyponatremia with outcomes such as mortality. Lower serum sodium levels have been associated with adverse clinical outcomes in most of the studies, independent of the presence of various confounders (Table 1). Hypernatremia has been generally under-emphasized, but it has also been found to be associated with a significant increase in mortality (Table 1) [7, 14].

In spite of the robust association of hypo- and hypernatremia with outcomes such as mortality, one cannot determine with certainty to what extent these associations may be biased by unmeasured confounders, especially since abnormal ADH secretion and consequently hyponatremia can occur as a result of various stress stimuli that can be difficult to quantify in observational studies. The emergence of specific pharmacologic inhibitors of the vasopressin receptor [29] has allowed the testing in clinical trials of the hypothesis that hyponatremia is causally involved in excess mortality, and hence its correction results in improved clinical outcomes. The short-term administration of vasopressin receptor antagonists was shown to result in a predictable correction of hyponatremia [30–33] and improvement in peripheral edema and various other clinical features of CHF [50, 51]. Based on such results, the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial was designed to test the hypothesis that correction of hyponatremia using tolvaptan (an oral selective V2 receptor antagonist [30]) versus placebo therapy on top of routine medical management of patients hospitalized with CHF results in improved all-cause mortality, cardiovascular mortality or CHF-related hospital admissions [52]. This study included 4133 patients treated with tolvaptan versus placebo for a minimum of 60 days and showed that none of the primary end points of the study were affected significantly by such treatment. While the results of the EVEREST study appear to refute the hypothesis invoking hyponatremia as a cause of increased mortality in CHF, it is unclear how the correction of hyponatremia would impact outcomes under different circumstances; patients with more severe hyponatremia or patients with hyponatremia unrelated to CHF may respond differently to the same treatment, and the longer duration of therapy with the same drug or effect of other interventions to correct hyponatremia may also result in different outcomes. At the present time, medical interventions including vasopressin receptor antagonists are indicated only for the correction of a biochemical abnormality (hyponatremia) but without a clear understanding of their impact on longer-term outcomes.

Water homeostasis, hyponatremia and hypernatremia in CKD

With advancing CKD, the kidney has a remarkable ability to maintain homeostasis, including the regulation of water balance [34]. In a study of 70 patients with advanced CKD (serum creatinine levels >10 mg/dL), serum sodium levels remained normal even until the point of the patients requiring initiation of renal replacement therapy [35]. The ability of the kidneys to adapt to changes in water intake does, however, diminish as both the maximum dilution and concentration of the urine gradually decline during the course of CKD (hyposthenuria), with the capacity to dilute typically being maintained longer than the capacity to concentrate [53]. Ultimately, as the patients reach end-stage kidney failure, the urine osmolality remains constant at ~300 mOsm/L (isosthenuria) irrespective of the actual volume of water intake. As a result, physiological factors other than the amount of water intake and urinary dilution and concentration will determine the amount of excreted water, and hence the development of hypo- and hypernatremia in patients with CKD. These include the amount of water delivered from the proximal tubule (which is typically decreased as a result of low glomerular filtration rate) and the amount of excreted solute, which can facilitate the development of both hypo- and hypernatremia in patients with

Table 1. Studies examining outcomes associated with serum sodium level in patients with normal kidney function[a]

Study	Patient population	Results	Other findings
Wald *et al.* [7]	$N = 53\,236$ patients hospitalized at a single medical center	Hyponatremia associated with increased mortality and length of stay and increased risk of discharge to a long-term facility. Hypernatremia also associated with higher mortality	Equal incidence of community and hospital-acquired hyponatremia (37.9 and 38.2%)
Waikar *et al.* [8]	$N = 98\,411$ patients admitted to two hospitals	Higher 1- and 5-year mortality risk associated with hyponatremia	Incidence of hyponatremia of 14.5%
Zilberberg *et al.* [9]	$N = 198\,281$ hospitalizations from 39 US hospitals	Hyponatremia associated with increased mortality, ICU admissions, mechanical ventilation, hospital length of stay and cost of care	Incidence of hyponatremia was 5.5%
Tierney *et al.* [10]	$N = 13\,979$ patients admitted over 46 months	Hyponatremia associated with increased in-hospital and long-term mortality	Incidence of hyponatremia at admission was 4%
Gill *et al.* [11]	$N = 104$ hyponatremic hospitalized patients compared to $N = 104$ randomly chosen normonatremic patients	Mortality and length of stay higher in the hyponatremic group	Mortality was higher if serum sodium fell during hospitalization
Clayton *et al.* [12]	$N = 108$ hospitalized patients with serum sodium <125 mEq/L compared to normonatremic patients	Mortality was higher in the hyponatremic group	Mortality depended on the etiology and not the severity of the hyponatremia
Lee *et al.* [13]	$N = 3784$ patients admitted to en emergency department	Lower serum sodium was associated with higher mortality	3.8% of patients had serum sodium <134 mEq/L. Most hyponatremic patients had hypovolemia
Mohammed *et al.* [14]	$N = 628$ patients presenting to an emergency department with decompensated CHF	Both hyponatremia and hypernatremia were associated with higher 1-year mortality rates	24% of patients had serum sodium <135 mEq/L. Lower serum sodium was associated with higher NT-proBNP levels
Gheorghiade *et al.* [15]	$N = 48\,612$ patients hospitalized with CHF from 259 hospitals	Hyponatremia associated with higher in-hospital and follow-up mortality and longer hospital stay	19.7% of patients had serum sodium <135 mEq/L
Gheorghiade *et al.* [16]	*Post hoc* analysis of $N = 433$ patients hospitalized with Stage 4 CHF and enrolled in a clinical trial	Persistent hyponatremia independently associated with increased mortality and re-hospitalization	23.8% of patients had hyponatremia; of these 68.9% had persistent hyponatremia
Rossi *et al.* [17]	*Post hoc* analysis in $N = 319$ hospitalized CHF patients treated with tolvaptan versus placebo	Significantly lower mortality of patients who had improvement in serum sodium levels	21.6% of patients had hyponatremia
Klein *et al.* [18]	*Post hoc* analysis in $N = 942$ hospitalized CHF patients treated with milrinone versus placebo	Lower sodium associated with increased in-hospital and 60-day mortality	Patients with lower serum sodium had more severe CHF
Lee *et al.* [19]	$N = 203$ patients with severe CHF	Hyponatremia was associated with increased CV mortality	Hyponatremic patients treated with ACEI had better outcomes
Goldberg *et al.* [20]	$N = 978$ patients with ST-elevation MI and no CHF	Hyponatremia associated with increased mortality and hospital readmission rates	11% of patients had serum sodium <136 mEq/L
Goldberg *et al.* [21]	$N = 1047$ patients with acute ST-elevation MI	Hyponatremia associated with increased 30-day mortality	12.5% of patients had serum sodium <136 mEq/L on admission and developed in 19.9% within 72 h

Continued

Table 1. *Continued*

Study	Patient population	Results	Other findings
Zilberberg *et al.* [22]	$N = 7965$ patients hospitalized with pneumonia	Hyponatremia associated with increased mortality, ICU admissions, mechanical ventilation, hospital length of stay and cost of care	8.1% of patients with pneumonia had hyponatremia
Borroni *et al.* [23]	$N = 156$ hospitalized patients with liver cirrhosis	Hyponatremia was associated with increased short-term mortality	29.8% of patients had hyponatremia
Lim *et al.* [24]	$N = 837$ patients listed for liver transplantation	Serum sodium level was not an independent predictor of mortality once adjusted for effect of GFR	GFR was measured by iothalamate clearance
Londono *et al.* [25]	$N = 241$ patients who received a liver transplant	Hyponatremia at the time of transplantation predicted 90-day post-transplant mortality	Long-term survival was not affected by serum sodium level
Heuman *et al.* [26]	$N = 507$ patients referred for liver transplantation	Hyponatremia was associated with higher mortality only in patients with MELD score <21	Persistent ascites and MELD score also predictive of mortality
Terzian *et al.* [27]	$N = 4123$ hospitalized elderly patients	Hyponatremia was independently associated with increased in-hospital mortality	Prevalence of hyponatremia was 3.5%
Bennani *et al.* [28]	$N = 2188$ patients admitted to an intensive care unit	Sodium <125 mEq/L was an independent predictor of mortality	Incidence of hyponatremia was 13.7%

[a]CV, cardiovascular; ICU, intensive care unit; MELD, model for end-stage liver disease; MI, myocardial infarction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

advancing CKD irrespective of the actual urine osmolality [54].

To the best of our knowledge, the incidence and prevalence of hypo- and hypernatremia in patients with different stages of CKD have not been studied at a population level until recently. In a recent study of 655 493 US veterans with non-dialysis-dependent CKD, the point prevalence of hyponatremia (serum sodium <136 mEq/L) was 13.5% and the point prevalence of hypernatremia (serum sodium of >145 mEq/L) was 2% [55]. During a mean duration of follow-up of ~5 years, however, 26% of all patients developed at least one episode of hyponatremia and 7% had at least one episode of hypernatremia, suggesting that these conditions and especially mild hyponatremia are common occurrences in patients with CKD. As shown in Figure 1A, the prevalence of hyponatremia did not correlate with the stage of CKD as it was essentially identical in patients with CKD Stages 3A and above. The prevalence of hyponatremia was higher in patients with CKD Stages 1 and 2, in whom the definition of CKD included the presence of significant proteinuria [56]. The prevalence of hypernatremia was about a magnitude lower overall compared to the prevalence of hyponatremia, but showed a significant increase with advancing stages of CKD (Figure 1B), supporting the observation that the kidney's concentrating ability is affected to a greater extent by advancing CKD than its diluting ability [53]. Overall, however, the prevalence of hyponatremia was significantly higher at all stages of CKD compared to the prevalence of hypernatremia.

The clinical characteristics associated with hyponatremia in our study were younger age, presence of diabetes mellitus, CHF, liver disease and depression, a higher estimated glomerular filtration rate (eGFR), blood glucose and white blood cell count and a lower serum albumin and blood hemoglobin. Characteristics associated with hypernatremia on the other hand were older age and lower eGFR, serum total bilirubin and blood glucose [55]. These results suggest that hypo- and hypernatremia may be affected by both the process of CKD and by the concomitant comorbidities occurring in patients with CKD. This study did not separate laboratory results obtained during an inpatient hospitalization versus an outpatient visit; hence it is unclear what the circumstances of occurrence were for these abnormalities.

Outcomes associated with hypo- and hypernatremia in CKD

Both hypo- and hypernatremia are associated with increased mortality in patients with normal kidney function (vide supra). These results should not be extrapolated to patients with various degrees of severity of CKD as it is unclear how the hypo- and isosthenuria developing with advancing CKD affect these outcomes when combined with various comorbid conditions that can impact water metabolism and outcomes. It is possible that hypo- and hypernatremia are more severe in CKD and hence they could be more deleterious; one could, however, also hypothesize that the chronic nature of the abnormalities affecting water metabolism in CKD allows the body to adapt

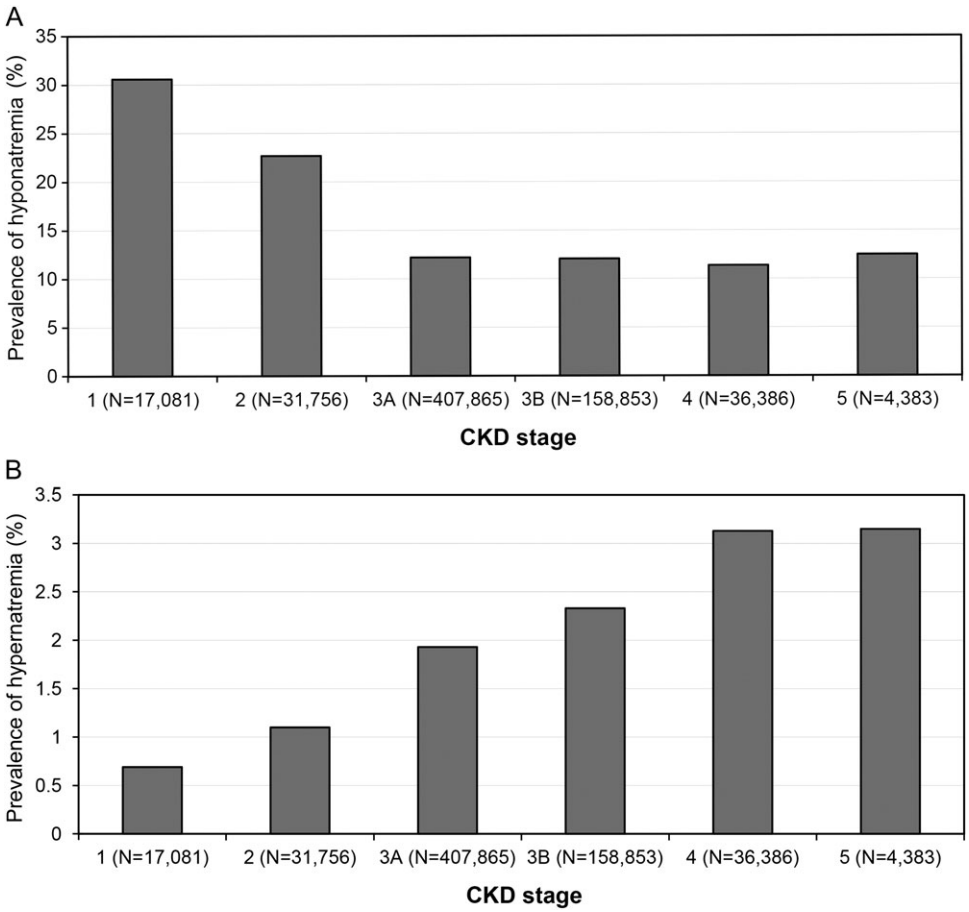

Fig. 1. Prevalence of hyponatremia (**A**) and hypernatremia (**B**) in patients with different stages of CKD in 655 493 US veterans with non-dialysis-dependent CKD. Results are based on data obtained from [55]. Note the different scales in the two panels.

to these consequences and hence their effects on outcomes could be diminished. We have recently examined the association of serum sodium levels with all-cause mortality in 655 493 US veterans with non-dialysis-dependent CKD Stages 1–5 (mean ± SD age was 73.9 ± 9.8 years, 87 and 9% of patients were white and black, respectively, and mean eGFR was 50.2 ± 14.1 mL/min/1.73 m^2) [55]. Both lower and higher time-varying serum sodium levels were associated with a significant increase in mortality, even after adjustment for various potential confounders (Figure 2). Mortality was lowest in patients with serum sodium levels in the 140–144 mEq/L range and showed a linear increase with increasing degree of severity of hypo- and hypernatremia. The association of hypo- and hypernatremia with mortality was present in all examined subgroups, including patients with and without CHF or liver cirrhosis [55], and also in patients with various stages of CKD (Figure 3). The magnitude of the association between hyponatremia and mortality did not appear to vary according to the severity of CKD (Figure 3). Interestingly, the association between hypernatremia and mortality appeared to diminish linearly with more advanced stages of CKD (Figure 3) [55]. The significance of this latter observation is unclear but suggests that perhaps there is indeed an element of adaptation to increased extracellular osmolality in patients with more advanced stages of CKD. As we mentioned previously, our study did not record the circumstances of serum sodium measurement (inpatient hospitalization versus outpatient), hence it is unclear to what extent the observed associations occurred in the context of acute illnesses. When comparing in parallel the associations of baseline serum sodium on longer term outcomes with the associations of time-varying serum sodium on short-term outcomes, the latter clearly showed much more robust associations [55], indicating that abnormalities in serum sodium are indeed either causing acute complications leading to higher short-term mortality or are simply potent surrogate markers of acute illness. Due to the observational nature of our study, we cannot establish causality in spite of the extensive adjustment for various potentially confounding comorbid conditions; such causality can only be proven if interventions of correcting serum sodium levels are shown to result in improved outcomes in CKD patients. Arguing in favor of a potential causal effect of dysnatremias on mortality was a recent study of maintenance hemodialysis patients enrolled in the Hemodialysis (HEMO) study, which reported a significant association of hyponatremia with mortality, even though in anuric dialysis patients the development of hyponatremia is unrelated to the pathological stimulation of ADH by underlying comorbidities [57]. Nevertheless, since in the anuric population, pre-dialysis hyponatremia could be a surrogate

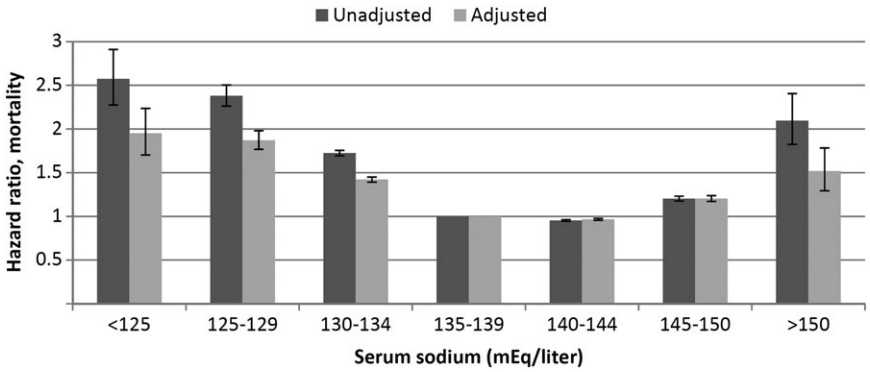

Fig. 2. Unadjusted and multivariable adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with various categories of serum sodium level in 655 493 US veterans with non-dialysis-dependent CKD. The group with serum sodium level of 135–139 mEq/L served as referent. Estimates are from time-dependent Cox model; multivariable adjusted models were adjusted for age, gender, race, geographic location, diabetes mellitus, atherosclerotic cardiovascular disease, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferases, total bilirubin, blood hemoglobin, glucose and white blood cell count. Results are based on data obtained from [55].

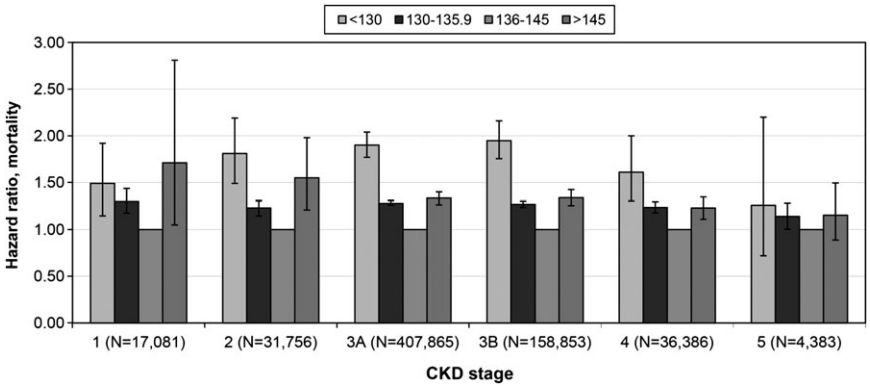

Fig. 3. Multivariable adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with mild (130–135.9 mEq/L) and moderate-to-severe (<130 mEq/L) hyponatremia and with hypernatremia (serum sodium >145 mEq/L) in 655 493 US veterans with different stages of CKD. Groups with serum sodium levels of 135–139 mEq/L served as referent. Estimates are from time-dependent Cox models adjusted for age, gender, race, geographic location, diabetes mellitus, atherosclerotic cardiovascular disease, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferases, total bilirubin, blood hemoglobin, glucose and white blood cell count. Results are based on data obtained from [55].

marker of increased inter-dialytic volume gain and consequently of a certain lifestyle of non-adherence with medical instructions, the need for interventional trials remains present for proof of a causal effect of hypo- and hypernatremia on mortality in CKD and end-stage renal disease.

Conclusions

Abnormalities in water homeostasis, manifested as hypo- and/or hypernatremia, are common clinical occurrences and are associated with adverse clinical outcomes. Patients with CKD can be affected by dysnatremias both because of the high prevalence of comorbidities that can result in dysnatremias in them and by the diminished ability of the failing kidneys to maintain an intact water homeostasis. Recent studies have suggested that the incidence and prevalence of dysnatremias, and especially those of hyponatremia, are substantial in patients with non-dialysis-dependent CKD and that they are associated with a significant increase in all-cause mortality. Hyponatremia appears to affect outcomes equally in patients with different stages of CKD, but hypernatremia appears to be associated with less severe outcomes in those with more advanced stages of CKD. Interventional trials are needed to establish if normalization of serum sodium levels can result in improving mortality rates in patients with CKD.

Acknowledgements. Dr Kovesdy is an employee of the US Department of Veterans Affairs. Opinions expressed in this paper are those of the author and do not necessarily represent the opinion of the US Department of Veterans Affairs.

Conflict of interest statement. None declared.

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Received for publication: 6.1.12; Accepted in revised form: 22.1.12

HHS Public Access

Author manuscript

Adv Chronic Kidney Dis. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Adv Chronic Kidney Dis. 2017 September ; 24(5): 332–341. doi:10.1053/j.ackd.2017.07.003.

Treatment of Disorders of Sodium Balance in Chronic Kidney Disease

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Abstract

Extracellular fluid volume expansion is nearly universal in patients with chronic kidney disease. Such volume expansion often overlaps with the syndrome of heart failure with preserved ejection fraction, which can not only lead to symptoms, but can also lead to further organ damage. Unique treatment challenges are present in this patient population, including low glomerular filtration, which limits sodium chloride filtration, intrinsic tubule predisposition to sodium chloride retention, and proteinuria. Additionally, pharmacokinetic considerations alter the disposition of diuretics in patients with chronic kidney disease and nephrotic syndrome. Maintaining extracellular fluid volume near to normal is often necessary for hypertension treatment in this population, but it may also help prevent progressive cardiovascular and renal damage. Although powerful diuretics can often accomplish this goal, this often comes at a cost of competing side effects. An approach to reduce extracellular fluid volume while avoiding side effects, therefore, requires a nuanced yet aggressive therapeutic approach.

Keywords

Diuretics; salt-sensitive hypertension; nephrotic syndrome; extracellular fluid volume expansion

Introduction

Disordered extracellular fluid (ECF) volume is nearly universal in chronic kidney disease (CKD), and typically presents with one of three common patterns. The most common includes mild ECF volume expansion, with salt-sensitive hypertension and left ventricular hypertrophy as predominant signs, but CKD can also present with more severe ECF volume expansion, typically together with the nephrotic syndrome. Less well recognized, at least today, is that CKD may also have components of salt wasting syndrome, sometimes severe

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The author declares that there is no conflict of interest.

enough to cause ECF volume contraction. The pathogenesis of these disorders will be reviewed, followed by a discussion of treatment.

Phenomenology of Salt Homeostasis in CKD

The rate at which kidneys excrete NaCl is related to the ECF volume and the blood pressure, which are therefore also related to each other. Although the nature of the relation between ECF volume and urinary NaCl excretion has been debated, Walser's summary of the literature (1) suggested that human urinary NaCl excretion, at steady state, is normally a *linear function* of the ECF volume in excess of a critical value. The relation between NaCl excretion and ECF volume, therefore, describes a 'renal function curve' as shown in Figure 1A. The supporting human experiments were often conducted during several days to weeks, so that the tested persons were at steady state, with NaCl excretion equal to the NaCl intake (minus minor extrarenal losses). Recent work by Titze and colleagues has added nuance to these precepts, showing that sodium chloride excretion is more variable than previously appreciated, when measured on a daily basis,[1] and that there is more sodium storage outside of ECF than previously understood.[2] Sodium storage in the skin associates with left ventricular hypertrophy in CKD.[3] Furthermore, in longer studies, it appears that some of the initial gain in ECF volume may dissipate over time.[4] Nevertheless, all agree that, in normal humans, 'on a long-term basis, indeed what goes in also comes out'[5], satisfying the law of mass balance. Further, even in the studies by Titze and colleagues, markers of ECF volume expansion remained suppressed when dietary salt intake is high,[4] suggesting that dietary NaCl loading does expand the ECF volume chronically; as noted below, this relationship is exaggerated in CKD.

Guyton and colleagues demonstrated that renal salt excretion plays a central role in setting the mean arterial pressure.[6] According to their analysis, which is related to, but distinct from Walser's, the relation between mean arterial pressure and urinary NaCl excretion at steady state is also nearly linear through a wide range of dietary salt intake; in fact, only very small changes in mean arterial pressure are required to produce substantial natriuresis (see Figure 1B). The relationship between mean arterial pressure and sodium excretion defines a different, but closely related, 'renal function curve',[6] and the effect of arterial pressure on urinary NaCl excretion has been called the *pressure natriuresis*.

These models are essentially phenomenological and do not provide specific insight into physiological control mechanisms. Both models, however, have been corroborated by experimental data and accurately describe renal salt homeostasis under many conditions. They also have interesting implications for understanding renal salt retention and renal salt-wasting disorders. For example, the slope of the relation between ECF volume and renal salt excretion (the 'time constant', Figure 1A) determines the speed with which an individual can adapt to a change in dietary intake. The slope appears to be reduced by aging and CKD (Figure 1A).[7] This means that it takes longer for the kidney to adapt to a change in dietary NaCl intake when renal function is compromised or an individual is aged (see Figure 2). Thus, if dietary salt intake is reduced suddenly, ECF volume will decline more in older individuals and in individuals with CKD than in younger individuals with normal renal function. Surprisingly, a reduced slope of the relation between ECF volume and dietary

NaCl intake also predicts that the ECF volume will be elevated when the dietary NaCl intake is normal or high in such patients.[8] This is the reason that individuals with CKD so often have ECF volume expansion and respond to dietary NaCl restriction with a marked decline in blood pressure. On the typical NaCl-rich 'Western' diet, the kidneys' slow responses shift the renal function curve downward and to the right (Figure 1B). If dietary salt intake is reduced suddenly, however, salt-wasting may occur.

Another important implication of the relation between ECF volume (or mean arterial pressure) and renal salt excretion is that salt-wasting may be present despite a preserved ability to reduce urinary salt excretion to negligible levels.[9] Clinical and experimental examples of salt wasting disorders in which urinary NaCl excretion can be very low include the Mendelian disease, Gitelman syndrome, which is caused by loss of function of the thiazide-sensitive NaCl cotransporter. This observation indicates that the diagnosis of salt wasting relies on the ability to estimate the extracellular fluid volume precisely. Because such determinations are nearly always imprecise clinically, the diagnosis of subtle renal salt wasting may be difficult.

Diuretics in CKD

Loop diuretics are typically drugs of first choice for treating ECF volume expansion in CKD, as discussed below. As shown in Figure 3, CKD alters the effectiveness of these diuretics in several ways. First, loop (and thiazide) diuretics are organic anions that reach their sites of action in the lumen of the thick ascending limb via secretion along the proximal tubules. The primary transport proteins involved, at the basolateral membrane, are organic anion transporters. Deletion of these proteins in mice produces diuretic resistance by inhibiting diuretic secretion into the tubule lumen.[10] These transport processes are relatively nonspecific, and a single transporter type can facilitate the movement of a variety of similarly charged molecules into the tubular lumen. Accordingly, any exogenous or endogenous substance that competes with a diuretic for one of these transport processes can potentially limit the efficient arrival of that diuretic to its site of action. Uremic anions are examples of endogenous substances that compete with loop and thiazide diuretics for tubular secretion and the dose response curve of these diuretics in CKD is shifted to the right (Effect A, in Figure 2).[11] This means that higher doses are required to present the same diuretic concentration to its active site.

A second, perhaps more important, effect of CKD, however, is related to the loss of NaCl filtration. Even though enhanced NaCl reabsorption by tubules is typically the primary cause of ECF volume expansion, as GFR declines, the amount of sodium chloride reabsorbed by each nephron must also decline, to maintain sodium chloride excretion equal to intake. This decline limits the effects of blocking sodium chloride reabsorption with diuretics. Viewed another way, the basal fractional sodium excretion increases as CKD progresses (Effect B in Figure 3A) to maintain sodium chloride balance. This means that, although the maximal *fractional* rates of NaCl excretion are preserved in CKD (Figure 3A), maximal absolute rates, those rates that actually determine ECF volume control, are decreased substantially (Effect C in Figure 3B). This means that more aggressive approaches, such as adding a thiazide or thiazide-like drug, are often necessary.

It should also be emphasized that, although there exists a 'ceiling' above which NaCl excretion does not increase, diuretic doses that exceed this ceiling can maintain drug levels in the natriuretic range for a longer period of time, making it appear that such a ceiling does not exist. This may be the reason that higher doses of loop diuretics may be more effective than lower ones in heart failure trials,[12] even when they exceed a theoretical 'ceiling'.

Hypertension in CKD

Most patients with CKD are salt-sensitive and have mild expansion of the ECF volume (described above). Yet this is often difficult to detect clinically, as homeostatic processes maintain the ECF volume close to normal until the glomerular filtration rate declines below 10 to 15 mL/min/1.73 M^2. As described by the Guyton model, ECF and plasma volume expansion occurs with minimal edema because the accompanying hypertension causes pressure natriuresis, preventing further ECF volume overload, which would otherwise lead to edema (see below). Scribner and colleagues[13] found that the exchangeable sodium content of the body was highly correlated with lean body mass in normal individuals (r=0.993) and was higher in patients with stage 4–5 CKD than in age-matched controls (62.0 versus 59.5 mEq/kg lean body mass) on their typical diets. When the individuals with CKD were switched to a salt restricted diet (0.5–2 g sodium), the exchangeable sodium content fell into the normal range, and the blood pressure declined by 53/22 mm Hg. Much more recently, Campbell and colleagues[14] performed a double blind placebo controlled trial of salt restriction in CKD. Although they initially evaluated 538 patients, only 25 qualified for randomization, and 20 finished the protocol. High sodium, 60–80 plus 120 mEq/d given as a slow release pill, was compared with a low salt, 60–80 mEq/day, for 2 weeks. The low salt intake led to a drop in systolic pressure of 9.7 ± 10.3 SD mm Hg (by ambulatory recording, see Figure 4), and to a decline in ECF volume of 800 milliliters (P<0.001). This was also associated with a drop in proteinuria by 342 mg/day, even though both plasma renin activity and aldosterone concentration were increased by the low salt intake. The energy intake did not change.

Left ventricular hypertrophy (LVH) is common in CKD and also appears to be associated with ECF volume expansion. In a study of 104 patients with CKD, even stage 2 CKD was associated with excess ECF volume, and ECF volume excess correlated with left ventricular mass index.[15] As LVH is associated with poor prognosis in this population,[16] it is reasonable to recommend dietary sodium chloride restriction for most patients with CKD. The most recent KDIGO guidelines for individuals with CKD recommend restricting sodium intake to <2 g daily, unless contraindicated.[17]

Although dietary salt restriction is essential, it is often insufficient to control the blood pressure and ECF volume expansion in CKD. While the use of antihypertensive agents in this situation is beyond the scope of this review, several comments on diuretic usage, as a component of antihypertensive regimens, are warranted. Agarwal tested the effects of the loop diuretics furosemide and torsemide on blood pressure and ECF volume in patients with stage 2 and 3 CKD.[18] As in the studies noted above, these investigators found that ECF water was elevated in the individuals with CKD at baseline. Diuretics decreased ECF water, decreases that persisted for up to 3 weeks, leading to reductions in blood pressure. Yet the

blood pressure reductions lagged after reduction in the ECF volume. As with salt restriction, discussed above, diuretic-induced decreases in ECF water were associated with the elevations in plasma renin activity and aldosterone, but these were not sufficient to counteract the ECF volume depletion.

Although thiazides and thiazide-like drugs are typically viewed as more effective than loop diuretics to treat hypertension in individuals with normal kidney function, as GFR declines, this relationship may reverse. This belief has both theoretical and observational underpinnings. Thiazides typically increase Na^+ excretion to 5–7% of filtered load, while loop diuretics can increase it to 20–25%. As GFR declines, there effectiveness would be expected to decline proportionately (Figure 2). It has been noted[19] that, when the GFR is 10 ml/min/M^2, for example, an individual must excrete approximately 10% of the filtered Na load (200 mEq) to be in negative salt balance. As the typical limits for thiazide effects are 5–7%, one would not expect these drugs to be very effective. Additionally, some early studies confirmed low effectiveness of thiazides when kidney function was poor.[20,21] These considerations have led KDOQI to recommend thiazides for the treatment of hypertension only as long as eGFR is greater than 30 ml/minute/M^2.

Yet interest in the continued use of thiazides as CKD progresses has resurfaced recently, acknowledging the superiority of these drugs for hypertension in normal individuals. While large comparative effectiveness trials are lacking, Agarwal reviewed the smaller trials examining this issue.[22,23] These generally showed effects of thiazide type diuretics on blood pressure, despite substantial CKD, but several factors should be noted. First, like with loop diuretics, it may be necessary to increase the dose above that recommended for individuals with preserved kidney function. With normal renal function, for example, doses of chlorthalidone are typically recommended to be 12.5–25 mg/day.[24] In one small study where the chlorthalidone dose was titrated, individuals with eGFR of 20–45 ml/minute/M^2 received an average of 67.5 mg/daily to achieve blood pressure control.[25] The second is that several of these studies used thiazides as ‘add on’ treatment for individuals already using loop diuretics. Chronic treatment with loop diuretics activates compensatory processes in the distal nephron that may strikingly increase the percentage of filtered NaCl reabsorbed therein.[26] This may be one reason that adding a thiazide or thiazide-like diuretic to a regimen of loop diuretics in the setting of CKD has long been known to be effective.[27]

Edema in CKD

As noted, many times CKD is associated with mild ECF volume expansion, but not enough to cause substantial edema or other signs of congestion, even when patients approach the need for dialysis. This is because the resulting hypertension drives a pressure natriuresis. In other situations, however, when nephrotic syndrome of heart failure accompanies CKD, then ECF volume expansion is more severe and signs of peripheral and central congestion do occur. These two situations will be considered separately, although the mechanisms involved share many features.

Heart failure is typically categorized as associated with reduced and preserved ejection fraction. While these two syndromes are not entirely distinct, the categorization has proved useful, as the treatment approaches, and treatment successes, are quite different. In the

situation of heart failure with reduced ejection fraction, damage to heart muscle reduces cardiac output, leading to hypotension, which is sensed by the kidney and in the vascular system. This leads to activation of the efferent limb of body NaCl homeostasis. Specifically, a decrease in glossopharyngeal and vagal tone from the carotid and aortic receptors to the CNS leads to a rapid increase in sympathetic activity with associated activation of the renin angiotensin aldosterone axis and, when severe, nonosmotic release of vasopressin.[28] Additionally, a decrease in pressure at renal baroreceptors, and decreased NaCl delivery to the macula densa, increase renin secretion, and thereby angiotensin II and aldosterone. The resulting increase in systemic vascular resistance and renal sodium and water retention raises venous pressure and restores cardiac output, through the Frank-Starling mechanism. The purpose of these concerted actions, therefore, is to maintain the arterial circulatory integrity and restore the perfusion to the vital organs, but the price paid is expansion of the ECF volume; in this case, edema results because the ECF volume expansion does not raise the arterial pressure about its normal threshold (Figure 1). Therapy is targeted to the neurohormonal factors that contribute to these processes, as well as to the congestion itself, and it has been shown to improve outcomes.

The pathogenesis of heart failure with preserved ejection fraction (HFpEF) is much more poorly understood, and therapy is largely symptomatic. Yet many observers have suggested that, in this situation, CKD may play an important and pathogenic role by causing ECF volume expansion and hypertension, and by damaging the heart and the endothelium[29]. Yet, despite differences between the two major categories of heart failure regarding pathogenesis, and despite the fact that many treatments have not been found to benefit heart failure with preserved ejection fraction, diuretics play central roles in treatment of both types. Heart failure itself can be a diuretic resistant state, but the combination of CKD and heart failure presents unique challenges for diuretic therapy, as described below.

Nephrotic syndrome, with substantial ECF volume expansion, is another situation in which edema is present in CKD. Two processes that are not mutually exclusive may be involved. The first results directly from the hypoalbuminemia that is a core feature of the syndrome. The fall in plasma oncotic pressure alters the Starling forces, increasing the flux of fluid into the interstitial spaces, leading the circulation to be ‘underfilled’.[30,31] In this case, when the blood pressure declines below the renal ‘set point’, NaCl retention is triggered and edema results, much like in heart failure. Patients with minimal-change disease often have a contracted plasma volume and a stimulated renin angiotensin aldosterone system.[32] Alternatively, primary renal NaCl retention, resulting from intrinsic renal disease, can contribute to ‘overflow edema’, when renal NaCl retention is driven by intrinsic renal processes. Patients with diabetes and hypertension usually have an expanded plasma volume and a suppressed renin angiotensin aldosterone system[33]. Yet primary renal NaCl retention alone tends to cause hypertension, with escape from NaCl retention, as discussed above. Thus, even in this situation, a component of abnormal fluid transudation from the plasma into the interstitium is essential for edema to develop. Ebah and colleagues[34] detected increased interstitial pressures in CKD patients with edema, especially those in whom the duration was short.

Micropuncture studies of sodium-retaining animal models of the nephrotic syndrome[35,36] demonstrate pronounced NaCl reabsorption in the distal nephron and thick ascending limb. The proteinuric kidney of a rat model of unilateral nephrotic syndrome has an enhanced Na^+ reabsorption in the collecting duct[37] and diminished response to ANP,[38] compared with the non proteinuric kidney. Hyperaldosteronism reinforces NaCl reabsorption at these sites. Renin and aldosterone levels are highly variable in patients with the nephrotic syndrome.[39] There is also growing evidence that one cause of primary renal NaCl reabsorption in nephrotic syndrome is related to the proteins that are filtered by the abnormal glomerular basement membrane. These may include proteases that activate epithelial sodium channels directly, by cleaving them.[40–42] Knowing whether the edema is mostly ‘overflow’ or ‘overfill’ has substantial therapeutic implications.

Kapur and colleagues reported that ECF volume contracted (underfilled) patients had higher BUN, BUN/creatinine ratio, urine osmolality, and lower FeNa (<0.2%) than expanded (overflow) patients; treatment with diuretics alone, without volume expanders, such as albumin, proved effective and safe for the volume expanded group.[43] Especially in children with minimal change disease, however, in whom a more ECF volume contracted pattern is common, it is customary to treat resistant edema with albumin combined with loop diuretics, with the goal of achieving transient movement of fluid into the vasculature during the diuresis.[32]

Nephrotic syndrome itself presents unique challenges to diuretic treatment, regardless of the pattern. Animal studies demonstrate five mechanisms that could impair the responsiveness to loop diuretics in patients with the nephrotic syndrome, including 1) decreased delivery and/or decreased tubular secretion of the diuretic, 2) increased renal diuretic metabolism,[44] 3) decreased blockade of the Na-K-2Cl cotransporter by the diuretic,[45] and 4) increased NaCl reabsorption by other nephron segments. Clinical studies confirm that nephrotic patients have an impaired tubular response to loop diuretics. Hypoalbuminemia decreases the binding of furosemide to plasma proteins and thereby increases its volume of distribution.[46] The secretion of loop diuretics by the proximal tubule is reduced by hypoalbuminemia,[44] and albumin infusion into nephrotic patients increases renal furosemide excretion in the urine.[47] Early work suggested that premixing furosemide with albumin prior to intravenous injection amplified diuresis,[48] but this was not confirmed by some others.[49–51] A meta-analysis suggested minor and transient benefits of combining albumin with loop diuretics, but noted that the quality of data was poor.[52] Indeed, patients with a serum albumin exceeding 2 g/dL can typically deliver normal quantities of furosemide into the urine.[53] A more effective approach to diuretic resistance in such patients, especially when signs of volume expansion are present, is to attempt to limit albuminuria with an ACE inhibitor or ARB, while using aggressive loop diuretic regimens. As noted above, any maneuver that reduces ECF volume, including loop diuretics, will provide further reductions in proteinuria.[54] Nevertheless, especially for children who appear ECF volume contracted, and with few nephritic signs, combining albumin with loop diuretics remains reasonable.

Another potential cause of diuretic resistance in nephrosis is that albumin filtered through the abnormal glomerulus can restrict the interaction of furosemide with the Na-K-2Cl cotransporter.[55] In micropuncture studies of rats, adding albumin to the tubular perfusate of

the loop of Henle attenuated the response to furosemide, presumably because of binding to albumin, an effect reversed by co-perfusion with warfarin, which displaces furosemide from its albumin binding site.[56] Agarwal and colleagues,[53] however, found that displacing furosemide from albumin by co-administration of sulfisoxazole did not affect natriuresis in patients with the nephrotic syndrome, suggesting that this mechanism is not predominant. This study, however, was not definitive, as these patients did not have diuretic resistance.

As noted above, one other cause of primary sodium retention in nephrotic syndrome has received attention recently. Plasma proteins that are filtered abnormally by diseased glomeruli include proteases. It is well established that the epithelial sodium channel, ENaC, is activated when it is cleaved by a diverse group of proteases. This appears to be a physiological pathway, but when abnormal proteins are present in the tubule lumen, it may be activated pathologically.[42] This mechanism might help to explain the data presented above, suggesting that activated sodium transport along the collecting duct is important in nephrotic syndrome. It provides a rationale for treating patients with amiloride or triamterene, but adequate clinical studies to support this are lacking.

Salt wasting in CKD

During the last half of the previous century, salt wasting as a complication of CKD was widely discussed, and viewed as a substantial clinical concern.[9] Renal salt wasting connotes inappropriate Na and Cl losses in the urine. Because salt (used here to indicate NaCl) excretion is determined largely by the ECF volume and mean arterial pressure, as discussed above, the term *renal salt wasting* indicates that renal salt excretion continues at an ECF volume at which renal salt excretion normally ceases. Yet *renal salt wasting* does not necessarily imply unrelenting renal salt losses. For example, the diagnosis of renal salt wasting was often said to require persistent sodium and chloride losses in the face of symptomatic extracellular fluid volume depletion. Yet genetic disruption of several renal ion transport proteins, like the thiazide-sensitive NaCl cotransporter, NCC, in humans with Gitelman syndrome, leads to subtle salt wasting that is not associated with unremitting salt losses or even with easily perceptible extracellular fluid volume depletion, although the blood pressure is slightly low.[57]

*T*he phenomenon of salt wasting resulting from CKD was first described by Peters.[58] Later, the term *salt wasting nephritis* was proposed to characterize a minority of patients with CKD who lose large amounts of NaCl in their urine.[59] The majority of patients with CKD have only a modest tendency to waste salt, as indicated by the fact that they cannot reduce urinary NaCl excretion promptly during dietary salt restriction. Despite this, they often have ECF volume expansion, when consuming a ‘Western’ diet, as discussed above.

Several theories have been advanced to explain this salt wasting tendency. First, natriuresis may result from an increased osmotic load per nephron. The second involves compensatory adaptations from the reduced number of functioning nephrons. When the number of nephrons is reduced, the single nephron glomerular filtration rate of the remaining nephrons increases. An increased single nephron glomerular filtration rate increases sodium delivery to the proximal tubule, which increases sodium reabsorption along the nephron (the

phenomenon of glomerulotubular balance). Although glomerulotubular balance tends to maintain urinary salt excretion within the normal range, it cannot compensate fully for the rise in sngfr, so some excess of sodium may escape reabsorption.

A third mechanism involves damage to kidney tubules leading to defective salt transport. This mechanism is probably most prominent when massive salt wasting (see below) results from tubulointerstitial or medullary cystic disease and can resemble Addison's disease.[59] According to Bricker and colleagues,[9] many cases of salt wasting associated with CKD are reversible, if the dietary salt deprivation is imposed gradually. This type of salt-wasting tendency likely contributes to the predisposition to AKI in patients with CKD. Whereas mild sudden ECF volume depletion can elicit prompt sodium chloride conservation in normal settings, the patient with CKD will be more susceptible to AKI because NaCl excretion will persist for longer. This phenomenon also has implications for treatment with dietary salt restriction. While a NaCl restricted diet is recommended for CKD, it may be useful to implement this gradually, to avoid worsening of kidney function.

Massive salt wasting is a rare, but devastating complication of CKD that can lead to cardiovascular collapse and death. In contrast to the mild salt wasting described above, patients with this disorder waste salt even when dietary salt is high. Thorn and colleagues[60] described two patients who presented with progressive volume depletion, hemoconcentration, lassitude, and eventually shock. The patients were shown to have CKD and massive salt wasting. The adrenal glands were normal, and adrenal hormone replacement was not effective. The authors coined the term *'salt losing nephritis'* to describe this syndrome. Enticknap found that chronic interstitial nephritis disease, primarily of the renal medulla, was responsible for most cases of massive salt wasting.[61] Many patients also demonstrate cystic changes in the renal medulla, although the inherited medullary cystic disease can present in a very similar manner and might be confused with this presentation clinically. Patients with salt-wasting typically present with weakness and tiredness, together with polyuria and nocturia. Hundreds of millimoles of NaCl may be lost in the urine daily.[62]

Many patients with massive salt wasting and renal failure have tubulointerstitial disease, as noted above, and often medullary calcifications. Among the disorders reported to lead to salt wasting are the milk-alkali syndrome and hyperparathyroidism salt wasting.[63] Patients with the milk-alkali syndrome can develop profound extracellular fluid volume depletion owing to salt wasting, but renal salt wasting often improves following correction of the alkalosis and hypercalcemia. Thus, once the calcium and acid/base disorder are corrected, the patients will retain salt normally, falsely suggesting that depletion of the extracellular fluid volume did not result from renal salt wasting. Other interstitial renal diseases also lead to salt wasting on occasion. These include multiple myeloma,[64] analgesic nephropathy,[65] and amyloidosis.[64] Many of these have been associated with nephrocalcinosis.

Practical Approach to Treatment of Salt Retention in CKD

When a patient with CKD presents with signs and symptoms of ECF volume expansion, it is always important to determine first whether nephrotic syndrome is contributing. Nephrotic patients often tolerate aggressive diuresis quite well, especially if they appeared to be

'overfilled', as noted above. Most clinicians introduce a loop diuretic, as first line treatment for ECF volume expansion in CKD, although a thiazide may be a reasonable choice in the setting of hypertension. Starting doses of 40–80 mg twice daily are reasonable for patients with stages 3 and 4 CKD, with dose escalation thereafter.[66] Because both CKD and nephrotic syndrome are diuretic resistant states, the most frequent error in treating such patients is using a dose that is too low. Many clinicians use furosemide, although pharmacokinetic considerations, including longer half-life and better bioavailability, suggest that torsemide should be preferred. Based on the short half-life, most patients should receive the drug twice daily.

While equipotent doses of bumetanide to furosemide are typically cited as 1:40 in patients with normal kidney function, the ratio declines to 1:20, as a result of non-renal bumetanide clearance, in the presence of stage 4–5 CKD.[67] Many patients, especially if previously untreated, will experience a gratifying natriuresis and a return of the ECF volume towards normal, when diuretics are initiated. An approach for those who do not is provided in Figure 5. As noted, this includes dose escalation. A maximal oral dose of furosemide is 160–320 mg, depending on the severity of the CKD, but many clinicians would add second line agents before raising the dose this far.

As shown on Figure 5, an important tool can be the measurement of urinary Na^+ excretion during 24 hours (with creatinine collected to confirm the collection adequacy). This will indicate both that the patient is responding adequately to the diuretic, and that he or she is ingesting too much salt, when the value exceeds 120 mmol/day (which is equivalent to 2.8 grams of sodium). The treatment in this case is to reduce dietary salt intake. While adhering to strict sodium restriction is not always achievable, this simple 'biofeedback' can prove helpful.

When maximal doses of loop diuretics still are not effective, most physicians add a thiazide type drug. Metolazone has been popular in this setting, and data from several trials in heart failure argue for its effectiveness.[68] Yet there is also evidence that other thiazides are effective, as well.[27] Continued resistance in this setting often suggests further diagnostic evaluation, and may be an indication to initiate dialysis.

Acknowledgments

The author has received support from the following sources for some of this work: NIDDK R01 DK051496, R01DK054983, and VA Merit Review I01 BX002228-02.

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Clinical Summary

- Chronic kidney disease is most commonly associated with expansion of the extracellular fluid volume, which typically contributes to hypertension.
- Loop diuretics are often required to reduce extracellular fluid volume and correct hypertension, but thiazide and thiazide-like diuretics may be more useful than previously appreciated.
- Nephrotic syndrome presents additional challenges to diuretic treatment, owing to the hypoalbuminemia and albuminuria

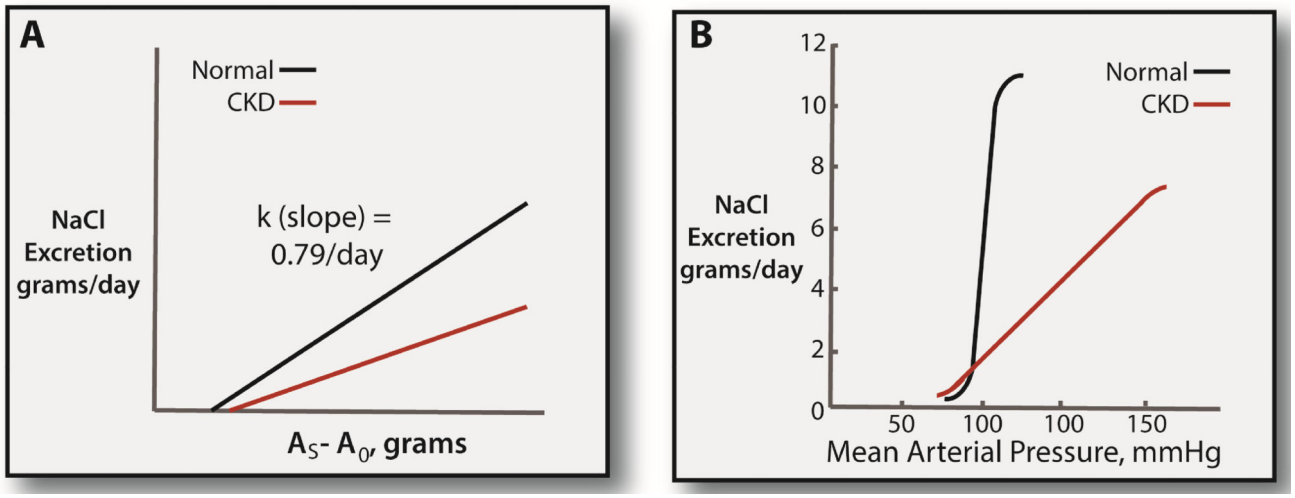

Figure 1. Renal function curves in normal individuals and CKD

Panel A: relationship between NaCl excretion and body sodium chloride content (A_S) above a basal value (A_0). This analysis is based on Walser.[69] The slope of the normal relationship (k, which is a time constant) is taken from Walser's review of the literature. The slope appears to be reduced by CKD. **Panel B:** Classic renal function curve, as drawn by Guyton and colleagues.[6] As argued by Guyton, CKD shifts the renal function curve downward and to the right, describing the increased salt-sensitivity in this population.

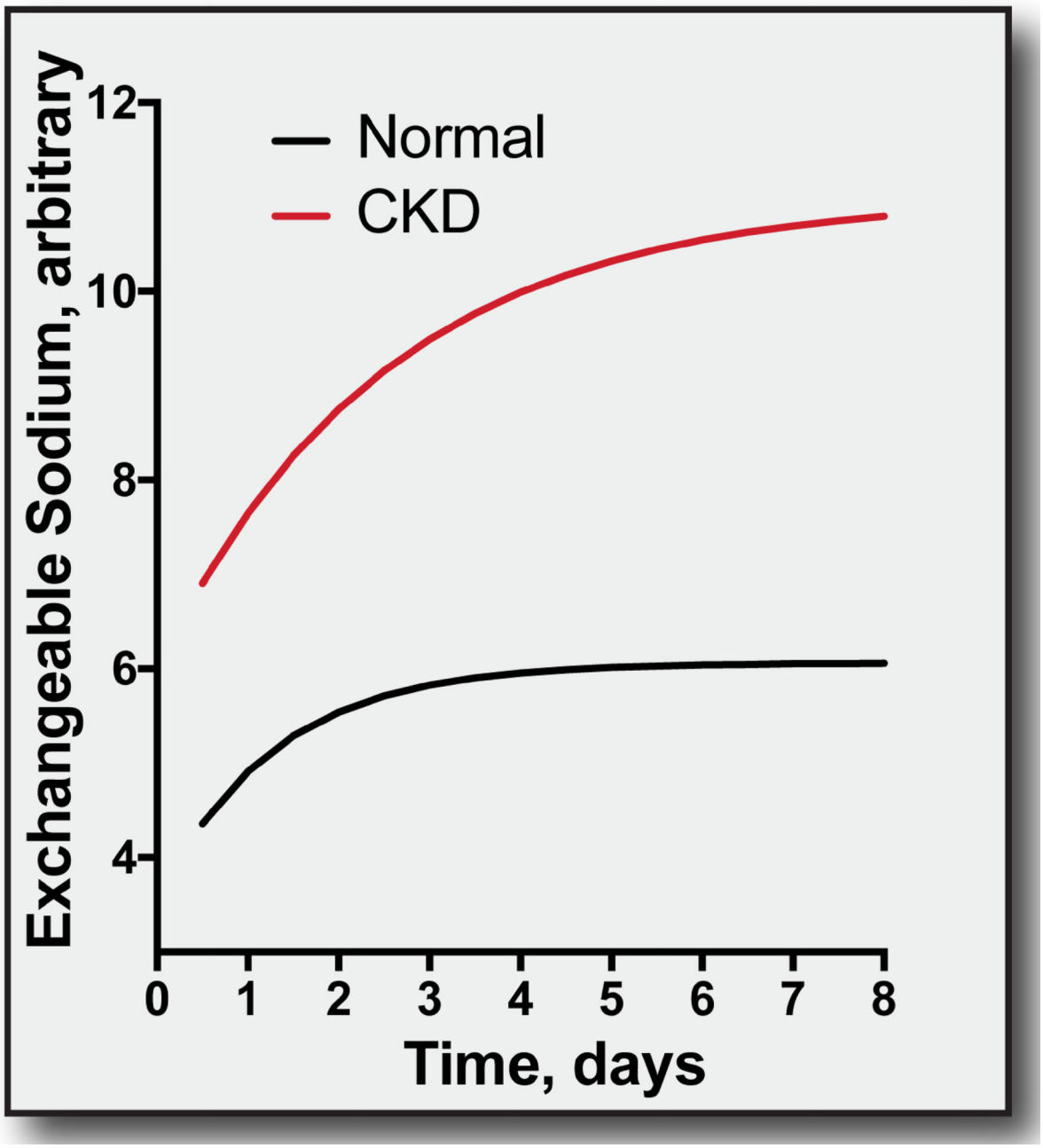

Figure 2. Effects of an increase in exchangeable sodium in normal individuals and CKD

This analysis is based on a summary of the literature,[69] and the equation,

$A_t - A_0 = \frac{I_2}{k} - \left[\frac{I_1 - I_2}{k} e^{-\mathrm{kt}}\right]$ described therein. At: body sodium at time t, A0: body sodium at the value that sodium excretion ceases, I2: intake of sodium at time 2, I1: intake of sodium at time 1, k is the time constant, defined as above. When dietary salt intake is increased, total body salt content rises approaching a new steady state. When kidney function is reduced, k is reduced, and the effect of a change is slowed and magnified. Note that longer observations suggest that the initial change in exchangeable sodium regresses

toward baseline,[4,5] as described by Guyton,[6], and likely resulting from pressure natriuresis. In CKD, however, easily detectable ECF volume expansion at steady state is still clear.[34]

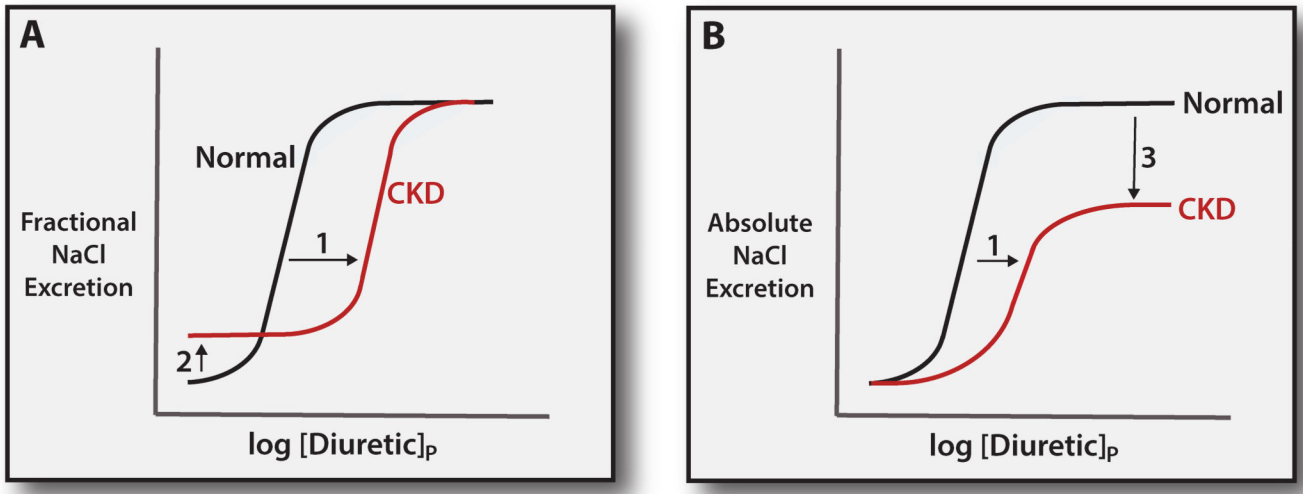

Figure 3. Mechanisms of diuretic resistance in CKD

Panel A: relationship between the log of the plasma diuretic concentration ($[diuretic]_p$) and fractional NaCl excretion. Note that CKD shifts the dose response curve to the right, owing to the impairment in diuretic secretion by the proximal tubule (**Effect 1**). At baseline, the fractional NaCl excretion is elevated in CKD, to preserve normal NaCl excretion (**Effect 2**). The ceiling effect, however, is preserved. **Panel B:** relationship between plasma diuretic concentration and NaCl excretion, expressed in absolute terms. Note that the dose response shift is also apparent in this analysis (**Effect 1**). In this case, however, the maximal (ceiling) effect is strikingly reduced (**Effect 3**).

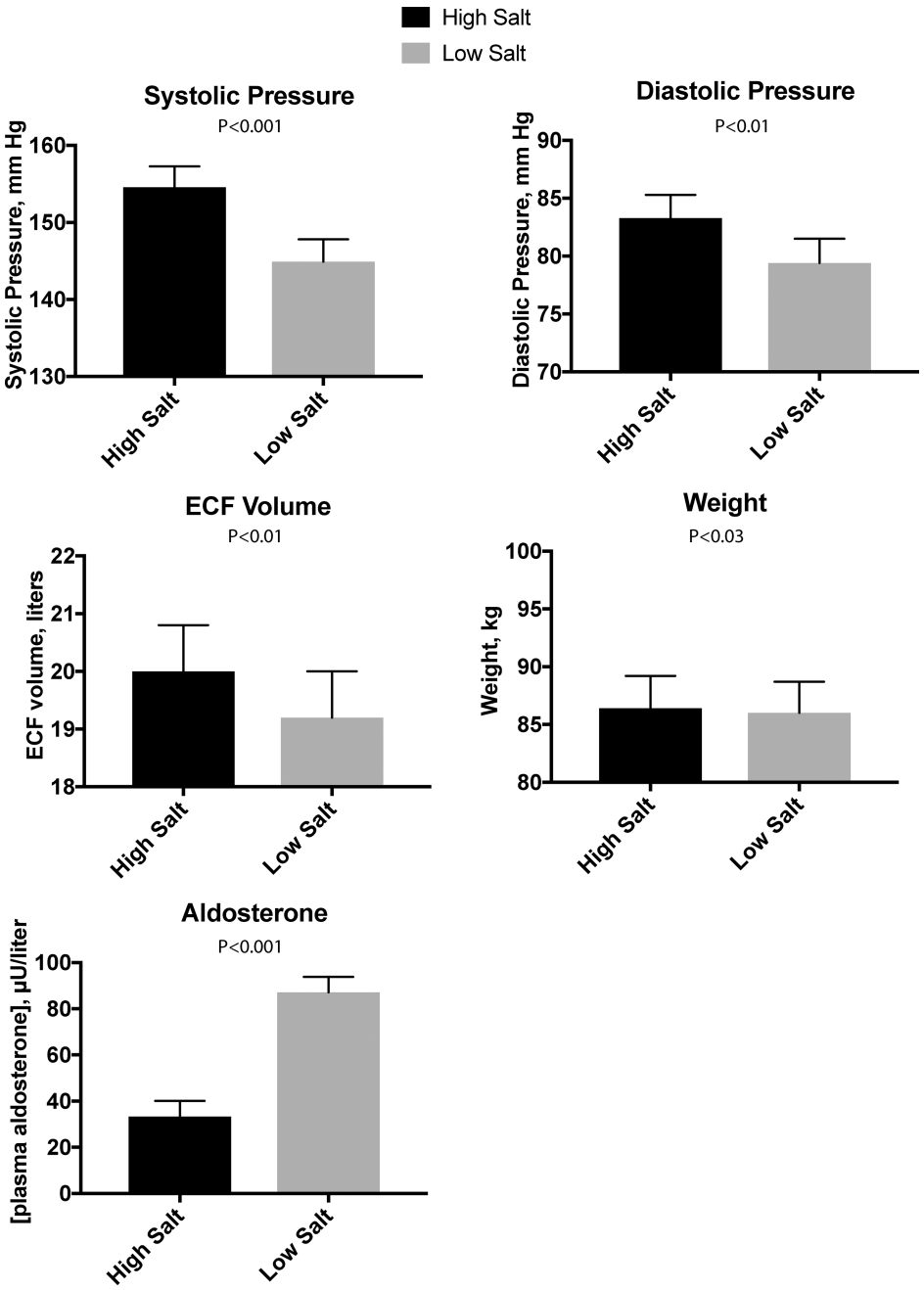

Figure 4. Effect of low salt diet in CKD

Panels show effects of randomized low salt diet in the setting of chronic kidney disease. In each case, the difference between high salt and low salt intake was statistically significant, with signs of ECF volume reduction being associated with declines in blood pressure. Data from.[14]

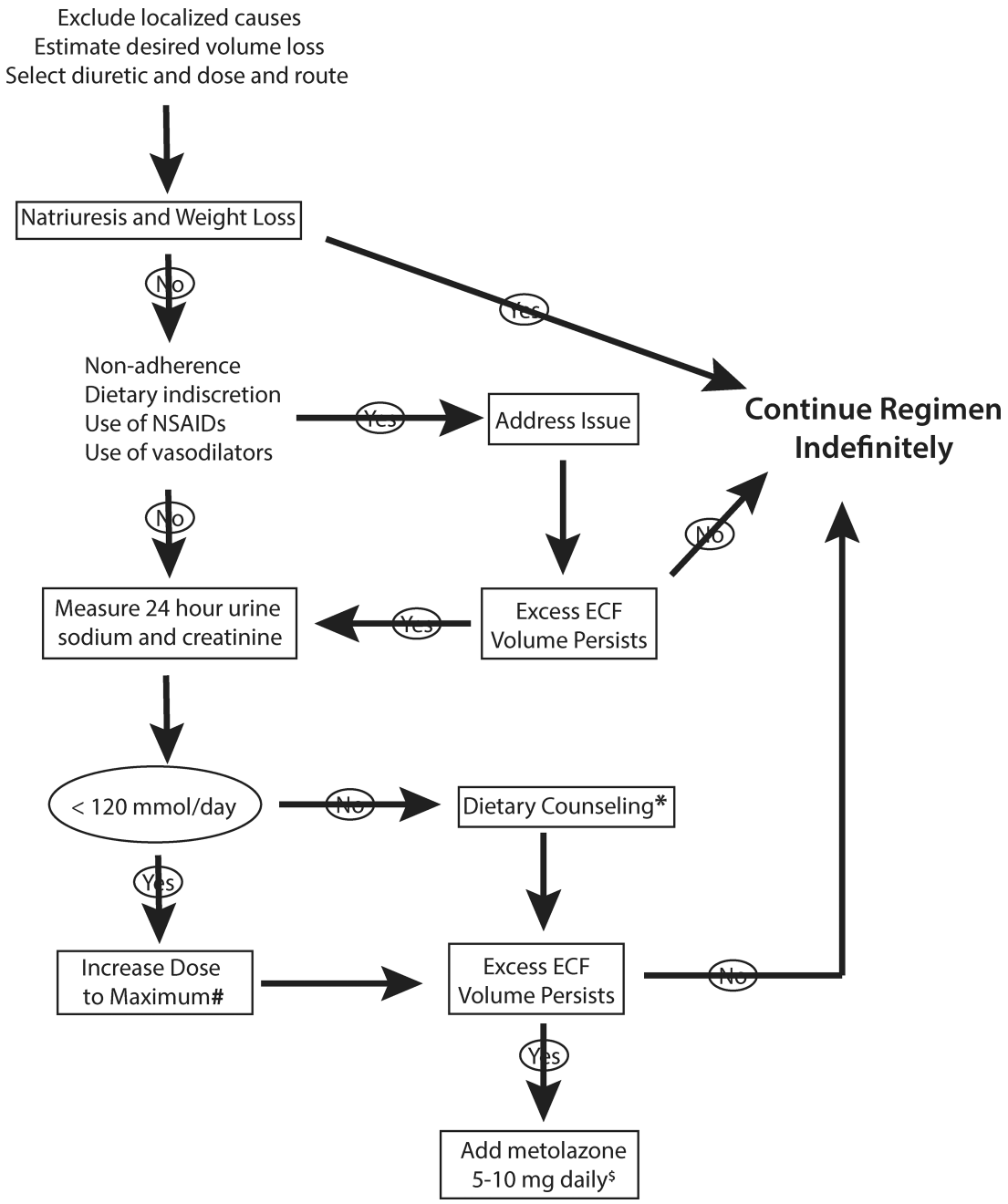

Figure 5. Algorithm for diuretic treatment in CKD

* indicates that dietary counseling may not be effective in reducing sodium intake, in which case more aggressive diuretic approaches are warranted. # indicates that dose ranges for loop diuretics are given in in the text. $ indicates that other thiazides are also effective, but metolazone is often selected as first line treatment.

Mild Chronic Hyponatremia in the Ambulatory Setting: Significance and Management

Helbert Rondon-Berrios and Tomas Berl†*

Abstract

Mild chronic hyponatremia, as defined by a persistent (>72 hours) plasma sodium concentration between 125 and 135 mEq/L without apparent symptoms, is common in ambulatory patients and generally perceived as being inconsequential. The association between increased mortality and hyponatremia in hospitalized patients in various settings and etiologies is widely recognized. This review analyzes the significance of mild chronic hyponatremia in ambulatory subjects and its effects on mortality and morbidity. It addresses whether this disorder should even be treated and if so, which patients are likely to benefit from treatment. The available approaches to correct hyponatremia in such patients in the context of recently published panel-generated recommendations and guidelines are described.

Clin J Am Soc Nephrol 10: 2268–2278, 2015. doi: 10.2215/CJN.00170115

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Introduction

Numerous studies have shown a significant association between hyponatremia and mortality in patients admitted to hospitals (1,2) or intensive care units (3,4). This association is consistent and well recognized across a number of etiologies and comorbidities, including heart failure (5), cirrhosis (6), neoplasms (7), and CKD (8). Hyponatremia has been felt to be a marker of severe and advanced disease rather than a direct contributor to excess mortality (9). We reviewed whether the association observed in ill hospitalized patients extends to ambulatory patients with mild chronic hyponatremia who have mild or no symptoms. However, the accompanying brain adaptation to hyponatremia makes them prone to morbidity and treatment-related complications. We present data regarding potential outcomes of mild chronic hyponatremia and its treatment that must be weighed against the benefit afforded by its correction.

Significance of Mild Chronic Hyponatremia

Mild Chronic Hyponatremia and Risk of Mortality

As a part of the baseline evaluation of the Copenhagen Holter Study, Sajadieh *et al.* (10) measured plasma sodium concentration (PNa) in a cohort study aimed at addressing the value of 48-hour Holter recording in risk assessment of 671 subjects without apparent cardiovascular disease. After adjustment for age, sex, smoking, diabetes, LDL cholesterol, and systolic BP, PNa<134 and <137 mEq/L were associated with hazard ratios (HRs) for the composite end point of all-cause mortality or first myocardial infarction of 3.56 (95% confidence interval [95% CI], 1.53 to 8.28; $P<0.05$) and 2.21 (95% CI, 1.29 to 3.80; $P<0.05$), respectively. This association was not driven by myocardial infarction. After excluding diuretic users, even PNa in the range of 135–137 mEq/L was found to be an independent predictor of the composite end point, with an HR of 2.39 (95% CI, 1.10 to 5.18; $P=0.03$).

Hoorn *et al.* (11) measured baseline PNa in 5208 subjects in the Rotterdam Study, a prospective cohort designed to assess risk factors for various ailments in the elderly population. With a prevalence of 7.7%, hyponatremia was an independent predictor of mortality, even after adjusting for demographics and comorbidities, with an HR of 1.21 (95% CI, 1.03 to 1.43; $P=0.02$).

Gankam-Kengne *et al.* (12) analyzed the significance of baseline PNa in the Dallas Heart Study aimed at identifying biologic, ethnic, and socioeconomic determinants of differences in cardiovascular health among 3551 subjects. The prevalence of hyponatremia was 6.3%. After adjustments for demographics, major comorbidities, and other factors, hyponatremia remained an independent risk factor for mortality, with an HR of 1.75 (95% CI, 1.08 to 2.81; $P=0.02$).

In a cross-sectional study, Mohan *et al.* (13) measured PNa in 14,697 adults who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004. At an estimated prevalence of 1.72%, hyponatremia was associated with an HR of death of 3.61 (95% CI, 2.31 to 5.63; $P<0.001$). Following Cox regression models adjusting for demographics, comorbidities, and other factors, a highly significant association persisted.

Taken together (Table 1), the data strongly support the view that hyponatremia is associated with an increased risk of mortality in outpatients, as it is in those that are hospitalized.

Mild Chronic Hyponatremia and Risk of Morbidity

Neurocognitive Deficits. The adaptive cerebral response to hyponatremia involves the loss of osmolytes, some of which are neurotransmitters (14), making the relationship between hyponatremia and central nervous system impairment biologically plausible. Several excitatory amino acids, such as glutamate, are lost in the adaptation to cell swelling, a process known as regulatory volume decrease (15,16). It is, therefore, not

Table 1. Studies reporting the association of mild chronic hyponatremia and mortality in ambulatory and community settings

Study	Study Design	Cohort Size	Definition of Hyponatremia (mEq/L)	Mean PNa ±SD (mEq/L)	Prevalence of Hyponatremia (%)	Mortality Rate (%) in the Hyponatremic Group	Mortality Risk (Adjusted HR)
Sajadieh *et al.* (10)	Prospective cohort	671	≤134	133[a]	2.1	43[b]	3.56 (95% CI, 1.53 to 8.28)
			≤137	136[a]	9.2	27[b]	2.21 (95% CI, 1.29 to 3.80)
Hoorn *et al.* (11)	Prospective cohort	5208	<136	133.4±2	7.7	51.6	1.21 (95% CI, 1.03 to 1.43)
Gankam-Kengne *et al.* (12)	Prospective cohort	3551	<135	133[a]	6.3	14.4	1.75 (95% CI, 1.08 to 2.81)
Mohan *et al.* (13)	Cross-sectional	14,697	<133 (1999–2002) and <136 (2003–2004)	132.3±2.6	1.72	11	2.43 (95% CI, 2.31 to 5.63)

PNa, plasma sodium concentration; HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Median PNa.
[b]Composite outcome of mortality or first myocardial infarction.

surprising that neurocognitive deficits are evident, even in apparently asymptomatic patients, when such changes are specifically probed for (17) (Table 2).

In a multifaceted landmark study, Renneboog *et al.* (18) performed neurocognitive testing in 16 patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH), with each serving as his/her own control before and after the treatment of hyponatremia. Attention deficits were evaluated by measuring reaction times and error numbers to a series of visual and auditory stimuli presented to the patients, who reacted with a simple motor response. When hyponatremic, the mean latency and error number were statistically higher, even compared with volunteers after moderate alcohol consumption. The threshold PNa at which attention deficits significantly increased was 132 mEq/L.

In a retrospective case-control study, Gosch *et al.* (19) administered the Comprehensive Geriatric Assessment, a standardized tool to screen for functional and cognitive disabilities, to 129 elderly patients with hyponatremia consecutively admitted to a geriatric unit and matched them for age and sex with 129 normonatremic controls. After multivariate analysis, the patients with mild chronic hyponatremia had significantly worse outcomes in the cognitive and functional tests of the Comprehensive Geriatric Assessment compared with controls.

Gunathilake *et al.* (20) evaluated cognitive function in asymptomatic community-dwelling individuals from the Hunter Community Study, a population-based prospective cohort study aimed to assess factors important in elderly health. Cognitive function was higher in individuals with a PNa of 135 mEq/L compared with those with a PNa of 130 mEq/L (95% CI, 1.56 to 7.79; $P=0.01$).

Gait Disturbances. Another component of the study by Renneboog *et al.* (18) evaluated gait by measuring the total traveled way (TTW) after a 10-second tandem walk with eyes opened over a pressure-sensitive calibrated platform. TTW was significantly longer during hyponatremia compared with TTW when PNa was restored to normal (Figure 1). The TTW in the hyponatremic group was even longer than that of volunteers after moderate alcohol intake.

Falls. To assess the significance of gait disturbances, Renneboog *et al.* (18) also studied the prevalence of falls in 122 consecutive patients with hyponatremia and 244 matched controls who presented to an emergency department during a 3-year period. Hyponatremia was associated with a higher prevalence of falls (21.3%) compared with normonatremic controls (5.3%), with an unadjusted odds ratio (OR) of 9.45 (95% CI, 2.64 to 34.09; $P<0.001$). After adjusting for demographics and covariates, the OR for falls in patients with hyponatremia markedly increased (OR, 67.43; 95% CI, 7.48 to 607.42; $P<0.001$). The threshold PNa at which fall risk significantly increased was 134 mEq/L. This observation has been substantiated by later reports (Table 3).

In another small retrospective study of psychiatric patients, Bun *et al.* (21) investigated the association between mild chronic hyponatremia and fall risk; 91 patients with hyponatremia were matched with 157 normonatremic subjects. Using backward stepwise logistic regression, hyponatremia was associated with an increased fall risk (OR, 4.38; 95% CI, 1.33 to 14.46).

The above-described study by Gunathilake *et al.* (20) found not only cognitive deficits but also, after adjusting for

Table 2. Studies reporting the association of mild chronic hyponatremia and neurocognitive deficits

Study	Type of Study	Cohort Size	Mean PNa ±SD (mEq/L)	Neurocognitive Assessment Tool	Outcomes of Hyponatremia
Renneboog *et al.* (18)	Crossover	16	128±3	Battery of attention tests[b]	Median latencies increased by 58 ms ($P<0.001$) and no. of errors increased 1.2-fold ($P=0.001$)
Gosch *et al.* (19)	Retrospective case control	258	128±3.2	MMSE and CC	In multivariate analyses, hyponatremia was a significant predictor for abnormal scores on the MMSE ($P=0.04$; OR, 1.96; 95% CI, 1.05 to 3.68) and CC ($P=0.02$; OR, 2.57; 95% CI, 1.19 to 5.55)
Gunathilake *et al.* (20)	Prospective cohort	2550	135 versus 130[a]	ARCS	Scores were, on average, 4.67 units significantly lower ($P=0.01$)

PNa, plasma sodium concentration; MMSE, Mini-Mental State Examination; CC, Clock Completion test; ARCS, Audio Recording Cognitive Screening tool; OR, odds ratio; 95% CI, 95% confidence interval.

[a]Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

[b]Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intermodal Comparison, Divided Attention, and Phasic Alert.

demographics and diuretic use, that a decrease in PNa from 135 to 130 mEq/L was associated with a 32% increase in fall risk.

Bone Fractures. Several studies have found that hyponatremia-associated gait instability, the most likely proximate cause for the high incidence of falls, also increases fracture risk (Table 4).

Gankam Kengne *et al.* (22) analyzed the association between bone fractures and hyponatremia in ambulatory elderly patients. They identified 513 patients with bone fractures and matched them for age and sex with 513 controls. Hyponatremia was present in 13% of subjects in the fracture cohort but only in 3.9% of controls ($P<0.001$), with an adjusted OR for cofounders of 4.16 (95% CI, 2.2 to 47.71).

Sandhu *et al.* (23) studied 364 patients who presented with a large bone fracture to the emergency room over an 18-month period and matched them with 364 controls; 9.1% of patients with fracture were hyponatremic compared with 4.1% in the fracture-free control group ($P<0.01$). By regression analysis, patients with hyponatremia were 2.5 times more likely to experience a fracture ($P=0.001$).

In a secondary analysis of a retrospective study aimed at the relationship between CKD and fractures, Kinsella *et al.* (24) found hyponatremia in 8.7% of patients with fractures but only in 3.2% of a fracture-free cohort ($P<0.001$). This study determined the OR after adjusting not only for age and CKD stage but also, T-score, osteoporosis risk factors, and treatment. After such adjustments, the OR remained significantly elevated at 2.25 (95% CI, 1.24 to 4.09), suggesting that hyponatremia, independent of bone mineral density (BMD), is a risk factor for fractures.

In the Rotterdam Study, hyponatremia was associated with an increased incidence of nonvertebral fractures, which remained significant (HR, 1.34; 95% CI, 1.08 to 1.68; $P=0.09$), even after adjusting for age, sex, body mass index (BMI), and multiple covariates (11).

In a retrospective case-control study, Tolouian *et al.* (25) assessed the prevalence of hyponatremia in 249 elderly patients admitted with hip fracture and compared it with the prevalence in 44 ambulatory controls concomitantly admitted for elective hip or knee replacement surgery. The prevalence of hyponatremia in cases and controls was 16.9% and 4.6%, respectively. After controlling for age, hyponatremia was associated with an increased hip fracture risk (OR, 4.8; 95% CI, 1.06 to 21.67; $P=0.04$).

Most recently, Jamal *et al.* (26) studied the association of hyponatremia with fractures among 5122 elderly community–dwelling men using data from the Osteoporotic Fractures in Men Study. Baseline prevalence of hyponatremia was 1.25%. Hyponatremia conveyed a higher risk of hip fracture (HR, 3.48; 95% CI, 1.76 to 6.87) as well as a higher risk for prevalent (HR, 2.78; 95% CI, 1.46 to 5.30) and incident (HR, 3.36; 95% CI, 1.36 to 8.27) morphometric fractures (*i.e.*, fractures identified by x-ray rather than from symptoms) compared with normonatremic subjects. After adjusting for cofounders, including falls and low BMD, the relationship between hyponatremia and fractures was not reduced.

It is of interest that the above-mentioned Rotterdam Study found an association between hyponatremia and fractures independent of falls. This argues against a primary role for falls, because vertebral fractures, which were also found to be associated with hyponatremia, are usually not caused by trauma.

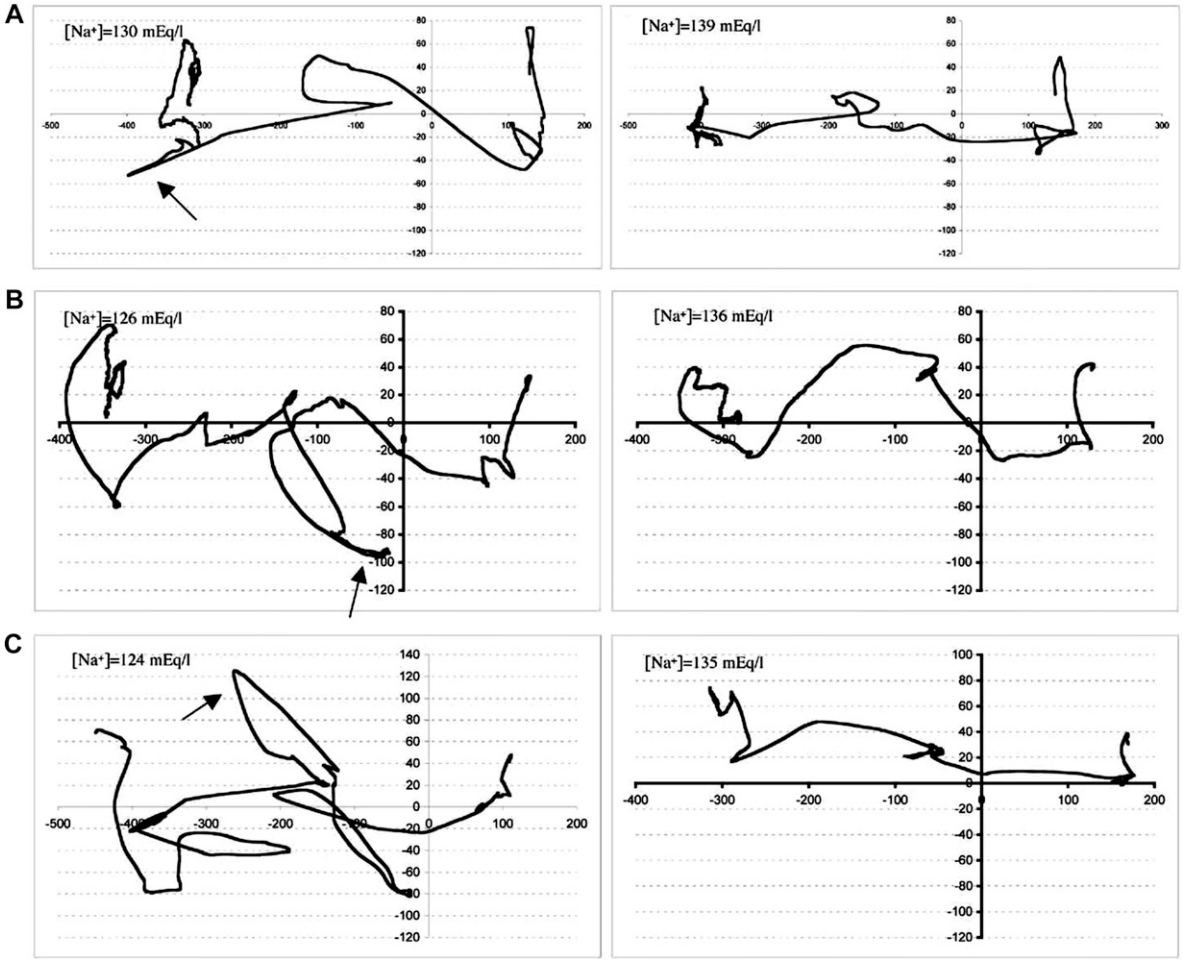

Figure 1. | **Mild chronic hyponatremia is associated with gait disturbances**. The recorded projection of the center of gravity over a pressure-sensitive calibrated platform or total traveled way (TTW) in three patients (A–C) after a 10-second tandem walk from right to left with eyes opened is shown. The left panel shows the TTW during mild chronic hyponatremia, and the right panel shows the TTW after correction of hyponatremia. Irregular paths of the center of pressure were observed in the hyponatremia condition (arrows). Reprinted from reference 18, with permission.

Table 3. Studies reporting the association of mild chronic hyponatremia and falls

Study	Type of Study	Cohort Size	Mean PNa ±SD (mEq/L)	Fall Risk (OR)
Renneboog *et al.* (18)	Cross-sectional	366	126±5	67.43 (95% CI, 7.5 to 607)
Bun *et al.* (21)	Retrospective case control	248	131.82±2.99	4.38 (95% CI, 1.33 to 14.46)
Gunathilake *et al.* (20)	Prospective cohort	2550	135 versus 130[a]	1.32 (95% CI, 1.04 to 1.64)

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

Osteoporosis. Verbalis *et al.* (27) have undertaken studies to better define the relationship between hyponatremia and bone metabolism using a rat model of SIADH. Hyponatremic rats had a reduction of bone mass of 30% compared with fluid-restricted controls that also received desmopressin but did not develop hyponatremia. There were no significant differences in serum calcium, parathyroid hormone, and urinary calcium excretion between groups. Microcomputed tomography showed a decrease in bone volume, cortical thickness, and trabecular number in all hyponatremic animals compared with controls. Hyponatremia increased the number of osteoclasts per bone area compared with controls, suggesting that increased bone resorption, rather than decreased bone formation, was the predominant mechanism.

Table 4. Studies reporting the association of mild chronic hyponatremia and bone fractures

Study	Type of Study	Cohort Size	Definition of Hyponatremia (mEq/L)	Mean PNa±SD (mEq/L)	All Fracture Risk (OR)
Gankam Kengne *et al.* (22)	Retrospective case control	1026	<134	131±3	4.16 (95% CI, 2.2 to 47.71)
Sandhu *et al.* (23)	Retrospective case control	728	<135	131±2	2.34 (95% CI, 1.24 to 4.35)
Kinsella *et al.* (24)	Retrospective case control	1408	<135	132.2±1.8	2.25 (95% CI, 1.24 to 4.09)
Hoorn *et al.* (11)	Prospective cohort	5208	<136	133.4±2	1.34[b] (95% CI, 1.08 to 1.68)
Tolouian *et al.* (25)	Retrospective case control	293	<135	a	4.8[c] (95% CI, 1.06 to 21.67)
Jamal *et al.* (26)	Prospective cohort	5122	<135	132.3±1.8	3.48[d] (95% CI, 1.76 to 6.87)

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Mean PNa not provided in the publication.
[b]Hazard ratio for nonvertebral fractures.
[c]OR for hip fracture.
[d]Hazard ratio for hip fracture.

In a follow-up study, Barsony *et al.* (28) examined the effects of hyponatremia on osteoclast number and activity. Exposure of murine monocytic and bone marrow monocyte culture cells taken from hyponatremic rats to low extracellular sodium concentration, while maintaining a normal extracellular osmolality by the addition of mannitol, directly stimulated osteoclastogenesis and osteoclast activity. These observations have been complemented by the work by Tamma *et al.* (29), which found that vasopressin receptor V1A and vasopressin receptor V2 (V2R) are present in osteoblasts and osteoclasts of wild-type mice and that vasopressin injected into these animals stimulated bone resorption by increasing osteoclast activity and inhibited bone formation by decreasing osteoblast activity through stimulation of V2R. This latter observation suggests that antidiuretic hormone (ADH) directly contributes to osteoporosis.

A cross-sectional study using the NHANES III database that investigated the association between hyponatremia in the general population ages 55 years and older and risk of osteoporosis provides the clinical significance to the above observations (27). After adjusting for age, sex, BMI, physical activity, 25(OH) vitamin D3 level, and diuretic use, hyponatremia (mean PNa was 133±0.2 mEq/L) was associated with an increased risk of osteoporosis at the femoral neck and total hip, with ORs of 2.87 (95% CI, 1.41 to 5.81; $P=0.003$) and 2.85 (95% CI, 1.03 to 7.86; $P=0.04$), respectively.

More recently, Kruse *et al.* (30) studied the association between hyponatremia and osteoporosis in a cross-sectional analysis of dexa scans from 1575 in- and outpatients and their concurrent PNas. Hyponatremia was associated with a lower BMD and bone mineral content at the total hip and lumbar spine in the unadjusted model but lost its significance when adjusted for sex, age, and BMI. However, using multiple regression analysis, a dose-response relationship was found between decreasing PNa and decreasing hip BMD, bone mineral content, and T-score.

In summary, increasing data have accumulated to support the contention that mild chronic hyponatremia, while apparently asymptomatic, is associated with cognitive deficits, gait disorders, and falls. These combined with an effect of hyponatremia to promote bone loss result in an increased fracture risk (31).

Management of Mild Chronic Hyponatremia

Despite the absence of randomized control trials assessing the efficacy of various treatment approaches to mitigate the above-discussed morbidities or the increased mortality associated with hyponatremia, consensus panels in the United States and Europe have put forth expert recommendations and clinical practice guidelines, respectively, for the treatment of such patients in various settings (32,33). We analyze herein the available approaches to treat mild chronic hyponatremia specifically for the ambulatory patient with SIADH (Figure 2). The primary goals in treating hyponatremia are to limit water intake and promote renal water excretion. The latter can be accomplished by increasing urine solute load, decreasing the medullary osmotic gradient responsible for water reabsorption, or inhibiting ADH actions (34).

Limitation of Water Intake

Because water intake in excess of the patient's ability to excrete it is central to the pathophysiology of hyponatremia, the limitation of water intake presents a cogent option for treatment. As such, it is the most common first step taken by most physicians. Fluid restriction should include all fluids and not just water. However, what degree of fluid restriction is needed, and will this approach consistently work on every such patient? To answer these questions, it is helpful to review the normal water balance, which is depicted in Table 5. Accordingly, the amount of fluid restriction required to achieve negative water balance should be less than the sum of urine and insensible losses. An alternative rule of thumb is to restrict fluid in an amount that is 500 ml less than the 24-hour urine volume (32).

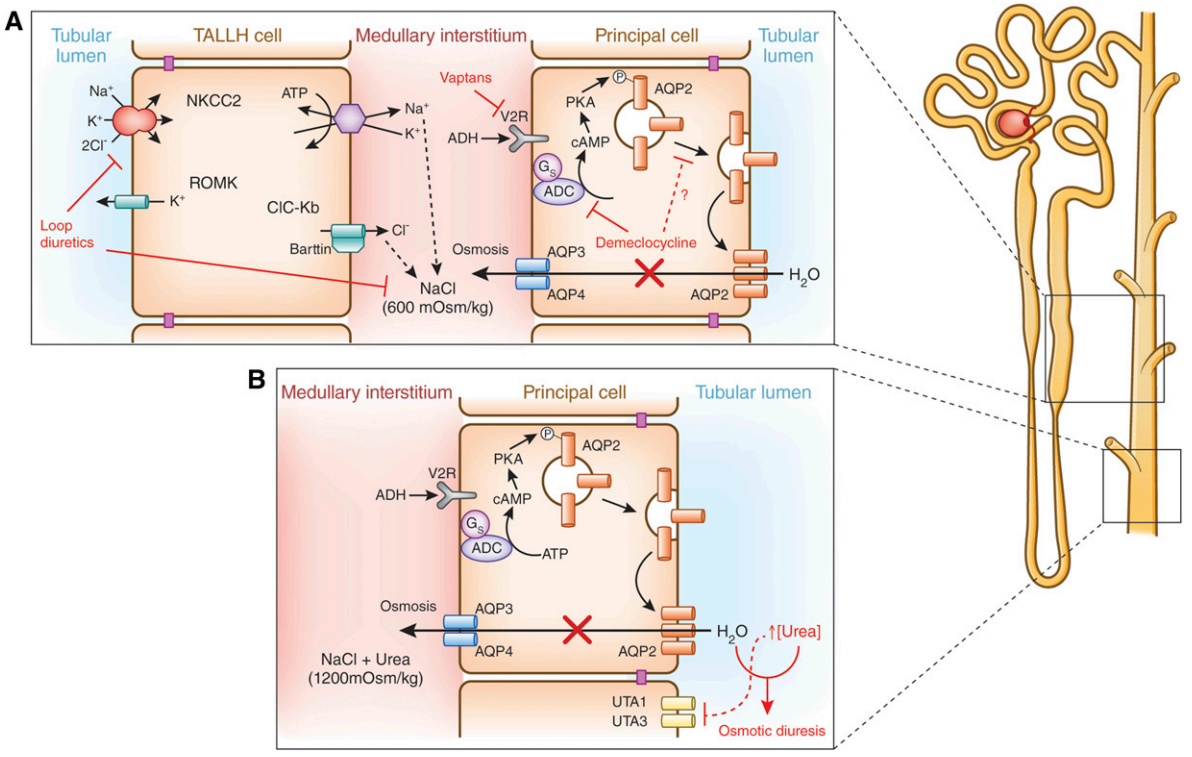

Figure 2. | **Mechanism of action of drugs commonly used to treat hyponatremia**. (A) ADH works by stimulating vasopressin receptors V2 (V2Rs) located in the basolateral membrane of the principal cells in the collecting duct (CD). V2Rs are G_s protein–coupled receptors that, when stimulated, increase cAMP production by adenylcyclase (ADC)-mediated conversion of ATP into cAMP. Elevated levels of cAMP activate protein kinase A (PKA), which in turn, phosphorylates stored aquaporin 2 (AQP2)-containing vesicles and targets them to the apical membrane of CD cells, increasing water permeability. The transport of NaCl into the medulla through the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2), located in the apical membrane of cells in the thick ascending limb of the loop of Henle, is essential for the generation of at least one half of the maximal medullary concentration gradient (600 mOsm/kg), which constitutes a main driving force for water reabsorption along the CD. Loop diuretics work in hyponatremia by inhibiting NKCC2 activity and therefore, interfering with the generation of a hypertonic medulla. Vaptans bind V2R, interfering with ADH action on its receptor. Demeclocycline inhibits ADC enzyme and, perhaps, also has some post-ADC actions. (B) The connecting tubule and cortical and outer medullary CD are impermeable to urea. The inner medullary CD (IMCD) is permeable to urea under the influence of ADH by activation of UTA1 and UTA3. Urea works as an osmotic diuretic in the IMCD, and, probably, along the connecting tubule and CD. In the IMCD, high luminal urea will tend to downregulate urea transporters. In addition, if luminal flow rate is high, there will be less time for urea transport. ADH, antidiuretic hormone; ClC-Kb, basolateral chloride channel; ROMK, renal outer medullary potassium channel; TALLH, thick ascending limb of the loop of Henle, UTA, urea transporters.

A more predictable way to estimate the amount of fluid restriction that is required to achieve changes in PNa is provided by the electrolyte-free water clearance (CeH_20) formula, which represents the amount of free water excreted by the kidneys over a 24-hour period:

$$CeH_20 = V \times \left(1 - \frac{UNa + UK}{PNa}\right)$$

where CeH_20 is the electrolyte-free water clearance, V is the urine volume in 24 hours, UNa is the urine sodium concentration, and UK is the urine potassium concentration.

If information about V is unavailable, ongoing CeH_20 and thereby, its effect on PNa can be assessed from a spot urine by calculating the urine to plasma electrolyte ratio [(UNa+UK)/PNa)]. A (UNa+UK)/PNa>1 indicates a negative CeH_20 (*i.e.*, net free water retention) and predicts a decrease in PNa. Conversely, a (UNa+UK)/PNa<1 reflects a positive CeH_20 (*i.e.*, net free water excretion) and predicts an increase in PNa. The recommended degree of fluid restriction that the ratio predicts is summarized in Table 6 (35).

Patients with SIADH often have (UNa+UK)/PNa>1 and therefore, a negative CeH_20. In such cases, tolerable fluid restriction is not likely to result in improvement of PNa, and additional therapies are usually needed. Other predictors of the likely failure of fluid restriction are urine osmolality >500 mOsm/kg, 24-hour urine volume <1500 ml, and increase of PNa of <2 mEq/L in the first 24–48 hours of fluid restriction <1000 ml/d (32).

Only one randomized study performed in children with acute meningitis addressed the effectiveness of fluid restriction. Fluid restriction was effective at increasing PNa in patients with hyponatremia but did not have any advantage in improving outcomes (36). Furthermore, in data obtained in a recent registry of >3000 subjects with hyponatremia, the increase in PNa observed with fluid restriction in the first 24 hours was not significantly different from that observed in untreated patients (37). PNa usually increases slowly and only by 1–2 mEq/L with fluid restriction alone. Fluid restriction is generally poorly tolerated because of an associated increase in thirst. When fluid restriction fails or is expected to fail, other measures require consideration.

Promoting Renal Water Excretion

Increasing Urine Solute Load.

Enteral Sodium Chloride. Urine solute excretion is a determinant of free water excretion (38). NaCl works in hyponatremia partly by increasing urine solute load, causing an electrolyte diuresis. However, NaCl is used in conjunction with loop diuretics for treating hyponatremia, where its primary role is the restoration of urinary sodium losses and prevention of negative sodium balance (39,40). No trials exist evaluating therapy with NaCl alone, and the very few reported cases using it are combined with loop diuretics. NaCl is available as 1-g (17 mEq sodium and 17 mEq chloride) tablets. Usual doses for NaCl tablets are 6–9 g daily in divided doses (*e.g.*, 2–3 g two or three times per day).

Urea. Urea recycling and its reabsorption in the inner medullary collecting duct (IMCD) by UTA1 and UTA3 transporters play an important role in the fine tuning of renal water reabsorption (41,42). However, urea is an ineffective solute; when its rate of excretion increases (*e.g.*, urea tablets, high-protein diet, post-ATN diuresis, or postobstructive diuresis), urea cannot be absorbed rapidly enough to equilibrate between the tubular lumen and the intracellular space of collecting duct (CD) cells. Under such circumstances, urea becomes an effective solute that obligates water excretion (43). Urea works in hyponatremia by inducing osmotic diuresis and decreasing free water reabsorption in the IMCD (44) and, probably, along the connecting tubule and CD (45). In an animal model, urea improved hyponatremia in SIADH by also decreasing the compensatory natriuresis that contributes to hyponatremia in this syndrome (46). The only clinical evidence for the efficacy of urea in the treatment of hyponatremia comes from case series (47–54). Decaux *et al.* (49) reported seven patients with the diagnosis of chronic SIADH who could not tolerate strict fluid restriction and were treated with oral urea 30 or 60 g/d. Despite normal water intake, urea corrected the hyponatremia in all seven patients (mean PNas pretreatment and during treatment were 115.6±6 and 136±3.5 mEq/L, respectively), with those with higher fluid intake requiring higher doses of urea (60 g/d). Although PNa rose significantly with urea treatment, the concentrations fluctuated widely, and this variation was related to fluctuations in daily water intake. No major side effects were noted after up to 270 days of treatment. Soupart *et al.* (53) also reported the use of urea in a case series of 13 patients with chronic hyponatremia from SIADH. PNa increased from a mean of 125±3 to 135±3 mEq/L at 1 year with the use of vaptans. The vaptans were then discontinued, allowing for recurrence of hyponatremia. Urea was then initiated for an additional 1 year, at the end of which mean PNa was again 135±2 mEq/L. Urea was well tolerated, and no major adverse events were reported. Current European guidelines favor its use as a second-line therapy (after fluid restriction) over the use of vaptans for the treatment of SIADH (33). However, there is no United States pharmacopeia formulation for urea, and it is not approved for this use by the Food and Drug Administration (FDA). Recommended doses are 30–60 g daily in divided doses (49). Urea has many advantages: it acts immediately and has minimal toxic effects, even at plasma concentrations of 193–301 mg/dl. If urine osmolality is high and renal function is well preserved, furosemide is preferred over urea, because it will take a high dose of urea to produce enough osmotic diuresis to be effective (40,55). Urea has been found to be especially effective in the treatment of the nephrogenic syndrome of inappropriate antidiuresis, a genetic disorder caused by activating mutations in the V2R, where vaptans are ineffective (56). BUN and urine osmolality are expected to increase with urea. Urea has a bitter taste, which limits its use, but combining it with sweet-tasting substances, such as orange juice, can alleviate this problem (33,44).

Table 5. Normal water balance

Source	ml
Water input	
Ingested water	1500
Food	800
Metabolic[a]	300
Total	2600
Water output	
Urine	1500
Sweat	100
Stool	200
Insensible losses[b] (TEWL[c] and respiratory)	800
Total	2600

TEWL, transepidermal water loss.
[a]Water generated in the body by the complete oxidation of carbohydrates, fats, and proteins.
[b]Water lost from the body that can be neither perceived nor measured directly.
[c]TEWL is the normal, constitutive loss of water vapor from the skin in the absence of sweat gland activity.

Table 6. Recommended degrees of fluid restriction on the basis of the urine to plasma electrolyte ratio

(UNa+UK)/PNa	Insensible Water Losses (ml)	Water Loss beyond Insensible Losses (ml)	Recommended Fluid Restriction (ml)
>1	800	0–800[a]	0
0.5–1	800	300–800	≤500
<0.5	800	300–800	≤1000

These estimates assume a urine volume of 1 L and a fluid intake closer to the maximal amount allowed by fluid restriction. UNa, urine sodium concentration; UK, urine potassium concentration; PNa, plasma sodium concentration. Modified from reference 35, with permission.
[a]Patients actually could have a negative net water loss (*i.e.*, free water retention) if the urine to plasma ratio is significantly high.

Decreasing Medullary Osmotic Gradient.

Loop Diuretics. The main driver for water reabsorption in the CD is the osmotic gradient generated by the renal medulla, which has tonicity of 1200 mOsm/kg at the level of the papilla. In the inner medulla, NaCl contributes to about 50% of this medullary hypertonicity, with urea contributing to the other 50%. The first step in NaCl transport to the medulla is through the $Na\text{-}K^{+}\text{-}2Cl^{-}$ cotransporter located in the apical membrane of the thick ascending limb of the loop of Henle cells. Loop diuretics inhibit this transporter, reducing NaCl delivered to the medulla and thereby, decreasing the medullary osmotic gradient necessary for water reabsorption in the CD and therefore, increasing free water excretion (57,58). The only clinical evidence for the efficacy of loop diuretics in the treatment of hyponatremia comes from case series, and all in combination with NaCl tablets (39,40,55,59). Of note, most of the patients in these case reports and case series improved their PNa with the combination of loop diuretics and NaCl tablets, despite a relatively normal fluid intake. Although infrequent, there have also been reports of hyponatremia in association with the use of loop diuretics (60,61). The dose of furosemide is 20–40 mg PO one time per day. Loop diuretics act immediately. They are not approved by the FDA to treat hyponatremia.

Inhibiting ADH Actions in the Kidney. Some causes of SIADH (*e.g.*, neoplasms and idiopathic) are not readily reversible. In such cases, consideration should be given to agents that antagonize the renal action of ADH: demeclocycline or vasopressin receptors antagonists.

Demeclocycline. Demeclocycline, a tetracycline derivative, decreases the activity of adenylcyclase and consequently, cAMP synthesis (62,63) and aquaporin 2 abundance in the IMCD (63), resulting in a reversible form of nephrogenic diabetes insipidus. Case series reported modest effects of demeclocycline on improvement of PNa in patients with hyponatremia (64). However, the only clinical trial in existence is a double-blind placebo crossover study with nine psychiatric patients with episodic or chronic hyponatremia caused by primary polydipsia (65). The investigators found no significant difference in the number of episodes of hyponatremia during the period of drug administration versus the placebo period. Nonetheless, demeclocycline is used in refractory cases of hyponatremia. Appropriate dosing of demeclocycline is 600–1200 mg/d in divided doses (62). The onset of action is usually 3 to 4 days (66). Demeclocycline is not approved by the FDA to treat hyponatremia. The use of demeclocycline has been associated with serious adverse reactions, such as skin photosensitivity, risk of superinfection, and nephrotoxicity, especially in patients with cirrhosis (67). Demeclocycline nephrotoxicity seems to be dose dependent, requiring slow dose titration and monitoring of kidney function. Given concerns for serious side effects, the European clinical practice guidelines on the diagnosis and treatment of hyponatremia recommend against its use (33).

Vasopressin Receptor Antagonists (Vaptans). Vaptans directly target the mechanism of hyponatremia in high ADH states by competing with ADH for binding at the V2R in the CD. Tolvaptan is the only oral vaptan approved by the FDA for use in the ambulatory treatment of euvolemic or hypervolemic hyponatremia. The ability of vaptans to increase PNa is amply documented. In fact, vaptans are the only interventions for the treatment of hyponatremia for which there are randomized control trials (*i.e.*, SALT1 and SALT2) (68) complemented by two well conceived meta-analyses (69,70). However, there is a risk of publication bias, because most trials on vaptans, with the exception of the SALT Trials, were done in relatively small numbers of patients, and almost all were sponsored by industry. In addition, there is almost a complete lack of head-to-head trials comparing vaptans with other used therapies. To avoid overcorrection, vaptans must be initiated and reinitiated as inpatient with frequent PNa monitoring. Tolvaptan is started at a dose of 15 mg daily. It may be increased to 30 mg after 24 hours and then, 60 mg after another 24 hours. To mitigate the rate of PNa increase, patients should not be fluid restricted for the first 24 hours. Long-term administration for up to 4 years suggests maintenance of effectiveness (71).

Several limitations must be considered in the use of vaptans. As is also the case with urea and demeclocycline, vaptans are contraindicated in hypovolemic hyponatremia and are not indicated in patients with severe neurologic symptoms, such as seizures, because they have not been tested in such subjects and the onset of changes in PNa is not rapid enough (at least 4–8 hours) to promptly address the symptoms. Vaptans are metabolized by CYP3A4, and therefore, caution should be exercised when coadministered with CYP3A4 inhibitors (*e.g.*, ketoconazole) or inducers (*e.g.*, rifampin), which increase or decrease drug levels, respectively. More recently, concerns regarding liver toxicity have emerged. The TEMPO 3:4 Study designed to determine the efficacy and safety of tolvaptan in the treatment of autosomal dominant polycystic kidney disease (72) reported an increase in liver function tests in the tolvaptan group compared with the placebo group. It is worth mentioning that the dose of tolvaptan used in this study was four times the dose used in the hyponatremia trials, in which no such toxicity was observed. The FDA recommends against using tolvaptan in patients with liver disease or for a period >30 days.

The development of osmotic demyelination syndrome (ODS) is always a concern when hyponatremia is corrected. Although PNa reached the hypernatremic range in some patients involved in the mentioned trials, ODS was not reported in any of them. Since then, in total, 12 patients with ODS in association with tolvaptan have been reported. Only two of those cases have been published (S.A.A. Harb and C. Alraies, unpublished data) (73). However, some other factors could have contributed to PNa overcorrection in the published cases. In the first case, tolvaptan was continued for 4 days, despite an initial increase of PNa from 126 to 142 mEq/L, with further overcorrection to 181 mEq/L by day 4 when tolvaptan was finally stopped. In the second case, the use of tolvaptan was in close temporal relationship with hypertonic saline use. The other 10 unpublished cases have been reported to the FDA (74). These adverse events generated a letter of warning from the producing company (75). A failure to respond to vaptans may occur in some settings (76). These include the presence of very high circulating ADH levels, a vasopressin-independent diluting defect (low distal delivery as a consequence of decreased GFR and enhanced proximal tubular reabsorption as in advanced heart failure or cirrhosis), excessive water intake, and the nephrogenic syndrome of inappropriate antidiuresis (56).

Notwithstanding the well established effects to increase PNa, there are no data to ascertain whether vaptans affect the above-described mortality or alter the risk for various morbidities associated with hyponatremia. Likewise, there is uncertainty as to whether vaptans decrease health resources use by affecting hospitalization rates and length of stay. There was a statistically insignificant trend in this direction in an analysis of the EVEREST Trial (77) and a significant effect in the SIADH subgroup in a *post hoc* analysis of the SALT Trials (78). However, for the average patient, the cost of vaptans remains an impediment for their use (79). The lack of mortality and morbidity benefit coupled with concerns about efficacy and safety led the European practice guidelines committee to not recommend the use of vaptans in euvolemic hyponatremia and even recommend against its use in hypervolemic hyponatremia (33). This is in stark contrast to the recommendations of an expert panel that views the use of vaptans as a reasonable option in both settings (32). It should be noted that the latter panel was supported by funding from Otsuka America Pharmaceuticals Inc., the manufacturer of tolvaptan, and that a substantial proportion of the panel members also had funding from Otsuka America Pharmaceuticals Inc.

Conclusions

Mild chronic hyponatremia is not benign as previously thought and can directly contribute to increased morbidity and possibly, mortality (31,80). Although some of the above pathology is clearly related to hyponatremia, whether treating the disorder will reverse this sequence of events is not yet known. We are of the opinion that patients with mild chronic hyponatremia associated with unstable gait, recurrent unexplained falls, a high fracture risk, or severe osteoporosis might benefit from treatment. The benefits versus risks probably shift in favor of the long-term ambulatory use of tolvaptan when fluid restriction and all other therapies have failed. We recommend that future studies address the following issues: (*1*) the efficacy, safety, and tolerability of urea in the treatment of hyponatremia; (2) the efficacy and safety of vaptans compared with other therapies; and (*3*) the effects of vaptans and other therapies on meaningful patient outcomes, such as falls and fractures.

Disclosures

H.R.B. receives no financial support. T.B. was on the speaker's bureau of Otsuka America Pharmaceuticals Inc. He was also the principal investigator of the SALTWATER Trial, a trial that was sponsored by Otsuka America Pharmaceuticals Inc. T.B. currently does not have any relationship with Otsuka America Pharmaceuticals Inc. He receives no payments, does not own any stock, and has no other conflicts of interest.

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Published online ahead of print. Publication date available at www.cjasn.org.

High and low sodium intakes are associated with incident chronic kidney disease in patients with normal renal function and hypertension

see commentary on page 776

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The association between salt intake and renal outcome in subjects with preserved kidney function remains unclear. Here we evaluated the effect of sodium intake on the development of chronic kidney disease (CKD) in a prospective cohort of people with normal renal function. Data were obtained from the Korean Genome and Epidemiology Study, a prospective community-based cohort study while sodium intake was estimated by a 24-hour dietary recall Food Frequency Questionnaire. A total of 3,106 individuals with and 4,871 patients without hypertension were analyzed with a primary end point of CKD development [a composite of estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2 and/or development of proteinuria during follow-up]. The median ages were 55 and 47 years, the proportions of males 50.9% and 46.3%, and the median eGFR 92 and 96 mL/min/1.73 m^2 in individuals with and without hypertension, respectively. During a median follow-up of 123 months in individuals with hypertension and 140 months in those without hypertension, CKD developed in 27.8% and 16.5%, respectively. After adjusting for confounders, multiple Cox models indicated that the risk of CKD development was significantly higher in people with hypertension who consumed less than 2.08 g/day or over 4.03 g/day sodium than in those who consumed between 2.93–4.03 g/day sodium. However, there was no significant difference in the incident CKD risk among each quartile of people without hypertension. Thus, both high and low sodium intakes were associated with increased risk for CKD, but this relationship was only observed in people with hypertension.

Kidney International (2018) **93,** 921–931; https://doi.org/10.1016/j.kint.2017.09.016

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Received 17 February 2017; revised 17 September 2017; accepted 21 September 2017; published online 29 November 2017

KEYWORDS: chronic kidney disease; dietary sodium; hypertension

Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease and death.[1,2] Blood glucose control and hypertension management are strategies that have been applied to prevent the development and progression of CKD. Nonetheless, the prevalence of CKD is rapidly increasing worldwide. Because established CKD is an irrecoverable condition, identifying modifiable factors and applying early interventions are crucial for reducing the burden of CKD.

Dietary sodium intake has been repeatedly reported to have an influence on cardiovascular risk factors and outcomes in several patient groups. A high sodium diet is known to aggravate hypertension,[3–5] and studies have shown high sodium intake to be also associated with an increased incidence of cardiovascular diseases.[6–13] However, restriction in dietary sodium intake also activates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system.[14–16] Aggravation of insulin resistance has also been reported in subjects consuming low dietary sodium.[17] Accordingly, a recent investigation showed that survival of patients with type 1 diabetes can be reduced not only by high urinary sodium excretion but also low excretion.[13]

As hypertension is a major risk factor for CKD,[18] the clear connection between sodium intake and blood pressure also links dietary sodium to CKD.[19–21] However, its association with renal function is less well investigated and confounding. Although several studies have shown that high dietary sodium intake increases the risk of CKD development or progression,[13,22–25] some results failed to find significant connections to renal outcome.[22,26–30] In addition, although the adverse effects of increased dietary sodium on cardiovascular outcomes are more prominent in subjects with hypertension than in those without,[4,8,9] influence of hypertension on the relationship between sodium intake and CKD development is not known.

Therefore, in order to investigate whether dietary sodium intake affects CKD development, this study assessed a prospective community-based cohort of subjects with normal renal function with and without hypertension.

RESULTS

Baseline characteristics

The baseline characteristics of subjects with and without hypertension are shown in Tables 1 and 2, respectively. The median (range) of the subjects' ages were 55 (47–63) and 47 (43–56) years; the numbers of male subjects were 1581 (50.9%) and 2255 (46.3%); and the median (range) of estimated glomerular filtration rates (eGFRs) were 92 (81–100) and 96 (84–105) ml/min per 1.73 m^2 in subjects with and without hypertension, respectively. The average (range) dietary intake of sodium were 2.93 g (2.08 g–4.03 g) in subjects with hypertension and 2.93 g (2.09 g–3.95 g) in subjects without hypertension.

Stratification into quartiles was done according to the amount of dietary sodium intake for subjects with and without hypertension. The proportions of participants with diabetes did not differ, and eGFRs were comparable in each quartile group with and without hypertension. When comparisons were made among the dietary sodium intake quartile groups of subjects with and without hypertension, participants in the higher sodium intake groups tended to

Table 1 | Baseline characteristics of subjects with hypertension

		Quartiles of dietary sodium intake (g/d)				
Variables[a]	Total (*N* = 3106)	Q1 (*N* = 777) <2.08	Q2 (*N* = 776) 2.08–2.93	Q3 (*N* = 777) 2.93–4.03	Q4 (*N* = 776) >4.03	*P*
Dietary composition						
Na intake (g/d)	2.93 (2.08, 4.03)	1.56 (1.20, 1.82)	2.53 (2.32, 2.74)	3.40 (3.14, 3.67)	5.02 (4.44, 6.05)	<0.001
Demographic data						
Age (yr)	55 (47, 63)	57 (49, 64)	55 (47, 63)	54 (46, 62)	55 (46, 62)	<0.001
Male (%)	1581 (50.9)	295 (38.0)	382 (49.2)	444 (57.1)	460 (59.3)	<0.001
SBP (mm Hg)	134 (126, 146)	136 (126, 148)	134 (126, 146)	134 (126, 144)	134 (126, 146)	0.17
DBP (mm Hg)	90 (84, 96)	90 (84, 94)	90 (84, 96)	90 (84, 96)	90 (84, 98)	0.07
BMI (kg/m^2)	25.4 (23.2, 27.4)	25.0 (22.8, 27.3)	25.5 (23.4, 27.5)	25.5 (23.4, 27.3)	25.5 (23.5, 27.4)	0.04
Waist-to-hip ratio	0.92 (0.87, 0.96)	0.92 (0.87, 0.97)	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)	0.92 (0.88, 0.96)	0.01
Education (%)						<0.001
Low	1310 (42.5)	397 (51.8)	323 (41.7)	291 (37.6)	299 (38.9)	
Intermediate	675 (21.9)	160 (20.9)	181 (23.4)	158 (20.4)	176 (22.9)	
High	1098 (35.6)	210 (27.4)	270 (34.9)	324 (41.9)	294 (38.2)	
Income (%)						<0.001
Low	1325 (43.3)	401 (52.1)	320 (41.9)	287 (37.5)	317 (41.5)	
Intermediate	847 (27.7)	208 (27.0)	223 (29.2)	203 (26.5)	213 (27.9)	
High	890 (29.1)	161 (20.9)	221 (28.9)	275 (35.9)	233 (30.5)	
Married (yes)	2750 (88.9)	659 (84.8)	688 (88.9)	701 (90.6)	702 (91.3)	<0.001
Ever drink (%)	1695 (54.8)	351 (45.4)	427 (55.2)	456 (58.8)	461 (59.6)	<0.001
Ever smoke (%)	1310 (42.5)	249 (32.4)	307 (39.8)	354 (45.9)	400 (52.1)	<0.001
Exercise (MET, k)	8.8 (4.8, 16.4)	8.0 (4.4, 16.4)	8.5 (4.9, 16.1)	8.8 (5.0, 15.9)	10.0 (5.4, 17.1)	<0.001
Comorbidities (%)						
Diabetes	598 (19.3)	157 (20.2)	145 (18.7)	166 (21.4)	130 (16.8)	0.11
Dyslipidemia	97 (3.1)	22 (2.8)	24 (3.1)	30 (3.9)	21 (2.7)	0.56
CVD[b]	130 (4.2)	40 (5.1)	37 (4.8)	26 (3.3)	27 (3.5)	0.19
Laboratory parameters[c]						
Na (mmol/l)	143 (142, 144)	143 (141, 144)	143 (141, 144)	143 (142, 144)	143 (142, 144)	0.49
BUN (mg/dl)	14.1 (11.9, 16.7)	14.1 (11.7, 16.5)	14.1 (11.9, 16.7)	14.0 (11.8, 16.6)	14.2 (12.0, 16.9)	0.35
Creatinine (mg/dl)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	<0.001
eGFR (ml/min per 1.73 m^2)	92 (81, 100)	93 (81, 100)	92 (81, 101)	92 (80, 100)	93 (81, 101)	0.72
Hemoglobin (g/dl)	13.8 (12.7, 14.9)	13.4 (12.5, 14.6)	13.9 (12.8, 14.9)	14.0 (12.8, 15.1)	14.0 (12.9, 15.1)	<0.001
Glucose (mg/dl)	84 (79, 93)	83 (77, 92)	84 (79, 92)	86 (80, 95)	85 (79, 93)	0.001
HbA1c (%)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.1)	5.7 (5.4, 6.0)	0.86
Albumin (g/dl)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.5)	4.2 (4.1, 4.4)	0.08
Cholesterol (mg/dl)	193 (171, 218)	192 (170, 217)	193 (170, 217)	197 (173, 223)	190 (170, 215)	0.79
Triglyceride (mg/dl)	153 (112, 212)	146 (109, 199)	152 (111, 204)	159 (113, 228)	156 (115, 223)	<0.001
HDL-C (mg/dl)	43 (37, 49)	43 (37, 49)	43 (37, 50)	43 (37, 49)	43 (37, 49)	0.91
LDL-C (mg/dl)	115 (93, 137)	116 (93, 138)	115 (94, 139)	118 (95, 139)	111 (90, 134)	0.03
CRP (mg/l)	0.16 (0.08, 0.27)	0.16 (0.08, 0.26)	0.15 (0.08, 0.26)	0.17 (0.08, 0.31)	0.16 (0.08, 0.27)	0.66

BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; Na, sodium; Q, quartile; SBP, systolic blood pressure.

[a]All continuous variables are expressed as median (25th, 75th percentiles). The values expressed as mean and SD can be found in Supplementary Table S1.

[b]A history of cardiovascular disease was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.

[c]*P* for trend was conducted by using the Jonckheere-Terpstra test.

Table 2 | Baseline characteristics of subjects without hypertension

Variables[a]	Total (N = 4871)	Quartiles of dietary sodium intake (g/d)				P
		Q1 (N = 1218), <2.09	Q2 (N = 1218), 2.09–2.94	Q3 (N = 1218), 2.94–3.95	Q4 (N = 1217), >3.95	
Dietary composition						
Na intake (g/d)	2.93 (2.09, 3.95)	1.58 (1.25, 1.83)	2.54 (2.32, 2.74)	3.36 (3.14, 3.64)	4.83 (4.31, 5.87)	<0.001
Demographic data						
Age (yr)	47 (43, 56)	48 (43, 58)	47 (43, 56)	47 (43, 55)	48 (43, 57)	<0.001
Male (%)	2255 (46.3)	478 (39.2)	524 (43.0)	597 (49.0)	656 (53.9)	<0.001
SBP (mm Hg)	110 (102, 118)	110 (102, 120)	110 (102, 118)	110 (100, 118)	110 (102, 120)	0.02
DBP (mm Hg)	74 (70, 80)	74 (70, 80)	74 (70, 80)	72 (68, 80)	74 (70, 80)	0.06
BMI (kg/m^2)	23.9 (22.1, 25.9)	23.8 (22.1, 25.8)	23.9 (22.1, 25.7)	24.2 (22.1, 26.0)	24.0 (22.1, 26.0)	0.16
Waist-to-hip ratio	0.87 (0.81, 0.92)	0.87 (0.81, 0.93)	0.86 (0.80, 0.91)	0.86 (0.81, 0.91)	0.88 (0.83, 0.92)	<0.001
Education (%)						0.008
Low	1282 (26.4)	366 (30.2)	321 (26.5)	289 (23.8)	306 (25.2)	
Intermediate	1121 (23.1)	281 (23.2)	263 (21.7)	286 (23.6)	291 (24.0)	
High	2446 (50.4)	563 (46.5)	629 (51.9)	638 (52.6)	616 (50.8)	
Income (%)						<0.001
Low	1364 (28.4)	414 (34.7)	312 (25.8)	297 (24.5)	341 (28.6)	
Intermediate	1468 (30.6)	356 (29.8)	382 (31.6)	368 (30.4)	362 (30.4)	
High	1971 (41.0)	423 (35.5)	514 (42.5)	545 (45.0)	489 (41.0)	
Married (yes)	4454 (91.8)	1100 (90.6)	1106 (91.0)	1127 (92.9)	1121 (92.5)	0.11
Ever drink (%)	2609 (53.8)	586 (48.2)	630 (51.8)	687 (56.6)	706 (58.4)	<0.001
Ever smoke (%)	1956 (40.5)	426 (35.2)	446 (36.8)	510 (42.2)	574 (47.6)	<0.001
Exercise (MET, k)	7.9 (4.8, 13.4)	7.6 (4.7, 13.3)	7.9 (4.7, 11.9)	8.0 (5.3, 13.0)	8.5 (5.0, 15.5)	<0.001
Comorbidities (%)						
Diabetes	480 (9.9)	113 (9.3)	115 (9.4)	117 (9.6)	135 (11.1)	0.41
Dyslipidemia	94 (1.9)	22 (1.8)	28 (2.3)	21 (1.7)	23 (1.9)	0.74
CVD[b]	87 (1.8)	22 (1.8)	16 (1.3)	24 (2.0)	25 (2.1)	0.52
Laboratory parameters[c]						
Na (mmol/l)	143 (141, 144)	143 (141, 144)	143 (141, 144)	143 (141, 144)	142 (141, 144)	0.10
BUN (mg/dl)	13.7 (11.6, 16.1)	13.5 (11.5, 16.0)	13.7 (11.5, 16.0)	13.6 (11.6, 16.0)	14.0 (11.8, 16.5)	0.002
Creatinine (mg/dl)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	<0.001
eGFR (ml/min per 1.73 m^2)	96 (84, 105)	97 (84, 105)	97 (86, 105)	96 (84, 105)	96 (84, 105)	0.44
Hemoglobin (g/dl)	13.4 (12.4, 14.6)	13.2 (12.3, 14.4)	13.4 (12.5, 14.5)	13.5 (12.5, 14.7)	13.7 (12.6, 14.8)	<0.001
Glucose (mg/dl)	82 (77, 88)	81 (76, 87)	82 (77, 88)	82 (77, 88)	82 (77, 90)	0.001
HbA1c (%)	5.5 (5.3, 5.8)	5.5 (5.3, 5.8)	5.5 (5.3, 5.8)	5.5 (5.3, 5.8)	5.6 (5.3, 5.9)	0.17
Albumin (g/dl)	4.2 (4.0, 4.4)	4.1 (4.0, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.1 (4.0, 4.4)	0.11
Cholesterol (mg/dl)	186 (165, 209)	183 (163, 208)	187 (164, 211)	187 (165, 210)	186 (166, 210)	0.05
Triglyceride (mg/dl)	124 (94, 172)	122 (92, 170)	124 (94, 171)	122 (92, 171)	129 (96, 176)	0.04
HDL-C (mg/dl)	44 (38, 50)	44 (38, 51)	44 (38, 51)	44 (38, 50)	44 (38, 50)	0.79
LDL-C (mg/dl)	112 (93, 134)	111 (91, 132)	113 (94, 135)	113 (94, 133)	112 (92, 135)	0.27
CRP (mg/l)	0.13 (0.06, 0.22)	0.13 (0.06, 0.22)	0.13 (0.06, 0.22)	0.13 (0.06, 0.23)	0.13 (0.05, 0.23)	0.81

BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; Na, sodium; Q, quartile; SBP, systolic blood pressure.
[a]All continuous variables are expressed as median and 25th and 75th percentiles. The values expressed as mean and SD can be found in Supplementary Table S2.
[b]A history of CVD was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.
[c]P for trend was conducted by using the Jonckheere-Terpstra test.

be younger, male, to be more educated, to have a higher income, and to have a higher body mass index and waist-to-hip ratio. In addition, subjects with and without hypertension in the higher sodium intake groups more frequently had a history of smoking or drinking and were more physically active. Laboratory data assessment of subjects with hypertension revealed that creatinine, hemoglobin, glucose, and triglyceride levels tended to higher in subjects with higher dietary sodium intake. As for subjects without hypertension, the levels of blood urea nitrogen, creatinine, hemoglobin, glucose, total cholesterol, and triglyceride tended to increase in those with higher dietary sodium intake.

The total calorie, protein, fat, carbohydrate, and potassium intakes were significantly increased with higher sodium intake regardless of hypertension status (Figure 1).

Development of incident CKD

During a median (range) follow-up duration of 122.8 (68.9–143.0) months in subjects with hypertension and 140.0 (95.4–143.1) months in those without hypertension, CKD developed in 864 (27.8%) and 803 (16.5%) subjects, respectively.

Impact of dietary sodium intake on incident CKD

The Kaplan-Meier plots constructed for subjects with hypertension showed that the time to the development of

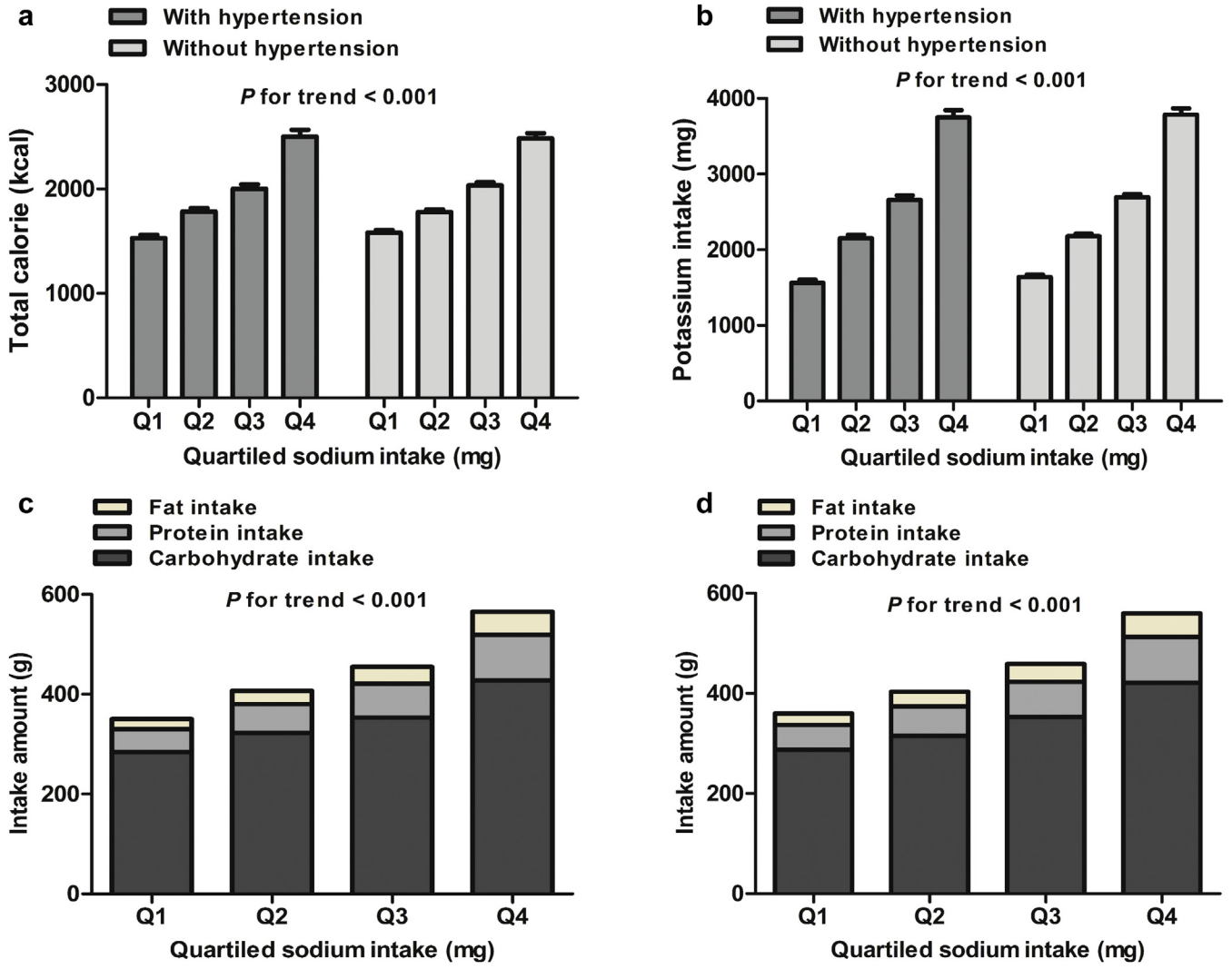

Figure 1 | Comparisons of dietary components according to quartiles of dietary sodium intake. Total calorie (**a**) is increased in parallel with increased amounts of dietary sodium intake in subjects with hypertension (*P* for trend <0.001) and those without hypertension (*P* for trend <0.001). Potassium intake shows similar trend of total calorie intake in both groups (**b**; *P* for trend <0.001). Fat, protein, and carbohydrate intakes increase according to greater intake of dietary sodium in subjects with hypertension (**c**; *P* for trend; fat, protein, and carbohydrate 0.620, 0.039, and <0.001) and those without hypertension (**d**; *P* for trend; fat, protein, and carbohydrate; <0.001, <0.001, and <0.001).

incident CKD was significantly longer in those consuming 2.93 to 4.03 g/d sodium (quartile [Q]3) than in those with-dietary sodium intake <2.08 g/d (Q1, $P < 0.001$) (Figure 2a). However, a significant difference was not found among subjects assigned to each quartile in those without hypertension (Figure 2b).

Multiple Cox proportional hazard regression models revealed that the risk of CKD development was significantly higher in subjects with dietary sodium intake <2.08 g/d (Q1: hazard ratio [HR], 1.35; 95% confidence interval [CI] 1.09–1.68; $P = 0.007$) and >4.03 g/d (Q4: HR, 1.38; 95% CI 1.10–1.73; $P = 0.005$) than in those who consumed 2.93 to 4.03 g/d sodium (Q3) among subjects with hypertension after adjusting for confounding variables. This significant increase in CKD risk was robust even when adjustments were made for the best fit model (Q1: HR, 1.32; 95% CI 1.08–1.61; $P = 0.008$; Q4: HR, 1.28; 95% CI 1.04–1.58; $P = 0.02$). However, there was no significant difference in the incident CKD risk among each quartile group of subjects without hypertension (Table 3).

The relationship between dietary sodium intake and incident CKD was further investigated in subgroups stratified by age, sex, and body mass index. Consuming <2.08 g/d (Q1: HR, 1.60; 95% CI 1.13–2.27; $P = 0.008$) or >4.03 g/d (Q4: HR, 1.86; 95% CI 1.33–2.60; $P < 0.001$) sodium significantly increased the risk of CKD development in subjects with hypertension younger than 60 years of age compared with those in the reference sodium intake quartile group (Q3). This significant relationship was also found in female subjects with hypertension (Q1: HR, 1.49; 95% CI 1.11–2.00; $P = 0.009$; Q4: HR, 1.74; 95% CI 1.26–2.41; $P = 0.001$). This relationship was significant regardless of body mass index (Table 4, Figure 3).

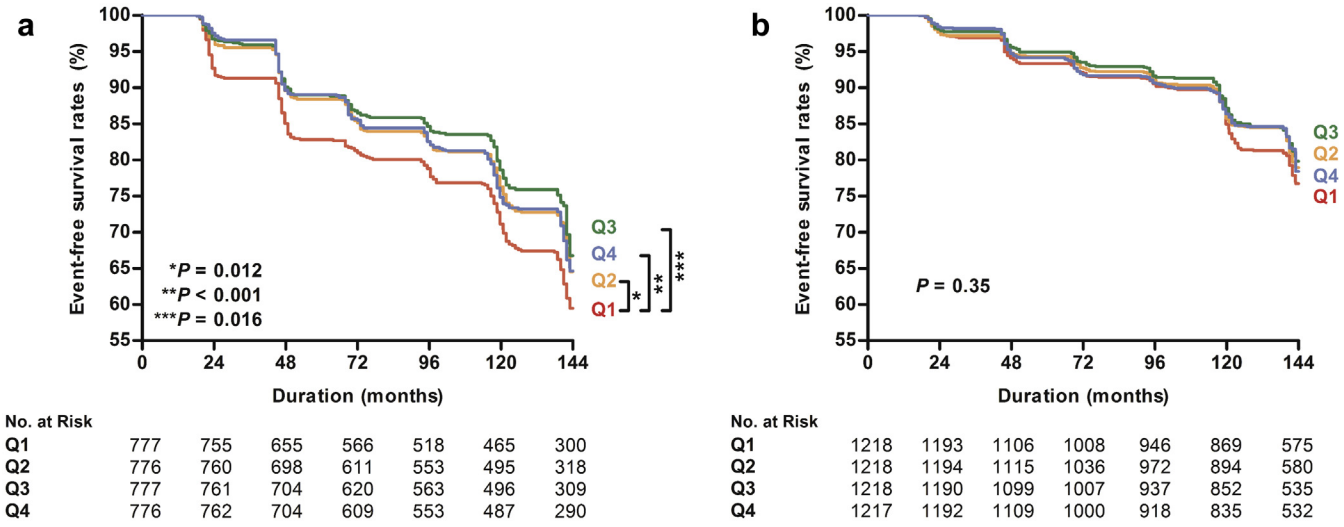

Figure 2 | Kaplan-Meier plot and incident CKD development according to dietary sodium intake in subjects with (a) and without (b) hypertension. *$P < 0.012$; **$P < 0.001$; ***$P = 0.016$. CKD, chronic kidney disease.

DISCUSSION

In this study, the relationship between dietary sodium intake and development of CKD was investigated in subjects with normal kidney function. Both high and low dietary sodium intake significantly increased the risk of CKD compared with moderate sodium intake in subjects with hypertension. However, the amount of sodium intake did not affect incident CKD development in subjects without hypertension. These findings suggest that a well-balanced dietary sodium intake is helpful in preserving renal function and that this effect is dependent on blood pressure status.

The relationship between dietary sodium intake and CKD development in this study was modified by hypertension status. This finding is in line with the results of recently published studies on the relationship of dietary sodium intake with cardiovascular disease. A prospective cohort study of 7543 subjects reported that the association between high sodium intake and coronary heart disease was confined to patients with hypertension or with increased concentrations of amino-terminal pro-brain natriuretic peptide.[8] In addition, a pooled analysis of 4 prospective studies showed an association between increased salt intake and cardiovascular events only in subjects with hypertension.[9] Although the modifying effect of hypertension status on the relationship between sodium intake and renal outcome has not been reported previously, a similar effect could be analogized from previous studies. High urinary sodium excretion was found to be associated with increased risk of CKD progression in patients with prevalent CKD in the Chronic Renal Insufficiency Cohort (CRIC) study.[23] However, the amount of urinary

Table 3 | Multivariate Cox proportional hazards regression analyses of association between dietary sodium intake and incident CKD

		Dietary sodium intake (versus Q3)						
		Q1		Q2			Q4	
	Models	HR (95% CI)	P	HR (95% CI)	P	Q3	HR (95% CI)	P
With hypertension	1	1.31 (1.08–1.58)	0.005	1.10 (0.90–1.34)	0.34	1.0 (reference)	1.20 (0.99–1.47)	0.06
	2	1.32 (1.07–1.63)	0.009	1.16 (0.94–1.43)	0.17		1.38 (1.11–1.71)	0.004
	3[a]	1.34 (1.08–1.67)	0.009	1.19 (0.96–1.46)	0.11		1.40 (1.11–1.75)	0.004
	Plus BMI[a]	1.35 (1.09–1.68)	0.007	1.18 (0.95–1.46)	0.13		1.38 (1.10–1.73)	0.005
	Best fit model[b]	1.32 (1.08–1.61)	0.008	1.12 (0.92–1.37)	0.25		1.28 (1.04–1.58)	0.02
Without hypertension	Model 1	1.04 (0.86–1.27)	0.70	1.05 (0.86–1.28)	0.66		1.01 (0.82–1.23)	0.94
	Model 2	1.05 (0.85–1.30)	0.66	1.09 (0.89–1.35)	0.40		0.97 (0.78–1.21)	0.80
	Model 3	1.05 (0.84–1.31)	0.67	1.09 (0.88–1.34)	0.44		0.95 (0.75–1.19)	0.65
	Plus BMI	1.05 (0.84–1.31)	0.66	1.09 (0.88–1.34)	0.44		0.95 (0.75–1.19)	0.64
	Best fit model[c]	1.06 (0.86–1.30)	0.59	1.06 (0.87–1.30)	0.56		0.97 (0.78–1.19)	0.75

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; Q, quartile.
Model 1: Adjusted for age, sex, and estimated glomerular filtration rate.
Model 2: Model 1 + protein intake, fat intake, waist-to-hip ratio, education, income, diabetes, cardiovascular disease, serum sodium, fasting glucose, and triglyceride.
Model 3: Model 2 + potassium intake, systolic blood pressure, marital status, smoking, exercise, hemoglobin, and serum albumin.
[a]Adjusted with spline term of systolic blood pressure.
[b]Adjusted for age, sex, estimated glomerular filtration rate, protein intake, fat intake, education, income, diabetes, triglyceride, exercise, and serum albumin.
[c]Adjusted for age, sex, estimated glomerular filtration rate, income, fasting glucose, triglyceride, and serum albumin.

Table 4 | Subgroup analyses of the relationship between dietary sodium intake and incident CKD

Variables		Hazard ratio (95% confidence interval)						
		Q1	*P*	Q2	*P*	Q3	Q4	*P*
With hypertension	Age <60 yr[a]	1.60 (1.13–2.27)	0.008	1.20 (0.86–1.67)	0.29	Reference	1.86 (1.33–2.60)	<0.001
	Age ≥60 yr	1.18 (0.88–1.57)	0.27	1.11 (0.84–1.46)	0.47		1.08 (0.78–1.48)	0.65
	Male[a]	1.15 (0.81–1.61)	0.44	1.01 (0.74–1.37)	0.96		1.08 (0.78–1.49)	0.64
	Female	1.49 (1.11–2.00)	0.009	1.33 (0.99–1.80)	0.06		1.74 (1.26–2.41)	0.001
	BMI <25.0 kg/m^2	1.41 (1.01–1.97)	0.046	1.23 (0.88–1.72)	0.22		1.44 (1.00–2.09)	0.05
	BMI ≥25.0 kg/m^2[a]	1.37 (1.02–1.83)	0.04	1.14 (0.87–1.51)	0.35		1.36 (1.02–1.80)	0.04
Without hypertension	Age <60 yr	1.19 (0.90–1.58)	0.22	1.22 (0.94–1.60)	0.14		0.91 (0.68–1.22)	0.53
	Age ≥60 yr	0.88 (0.61–1.28)	0.51	0.93 (0.65–1.32)	0.68		0.99 (0.68–1.44)	0.96
	Male	1.14 (0.78–1.65)	0.50	1.32 (0.95–1.83)	0.10		1.02 (0.72–1.43)	0.93
	Female	1.01 (0.76–1.33)	0.96	0.94 (0.71–1.24)	0.66		0.92 (0.67–1.26)	0.61
	BMI <25.0 kg/m^2	1.17 (0.88–1.55)	0.28	1.15 (0.88–1.50)	0.32		1.00 (0.74–1.34)	0.98
	BMI ≥25.0 kg/m^2	0.92 (0.63–1.34)	0.67	1.04 (0.73–1.47)	0.85		0.90 (0.62–1.29)	0.56

BMI, body mass index; CKD, chronic kidney disease; Q, quartile.
Adjustments were made for age, sex, estimated glomerular filtration rate, protein intake, fat intake, waist-to-hip ratio, education, income, diabetes, cardiovascular disease, serum sodium, fasting glucose, triglyceride, potassium intake, systolic blood pressure, marital status, smoking, exercise, hemoglobin, serum albumin, and BMI.
[a]Adjusted with spline term of systolic blood pressure.

sodium excretion did not increase the risk of CKD development in a cohort with normal kidney function enrolled in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study.[27] Considering that 85% of participants in the CRIC study were hypertensive, whereas only 10% of subjects in the PREVEND study had hypertension, there is a possibility that hypertension status could have played a role in the different effects of sodium intake on renal function decline.

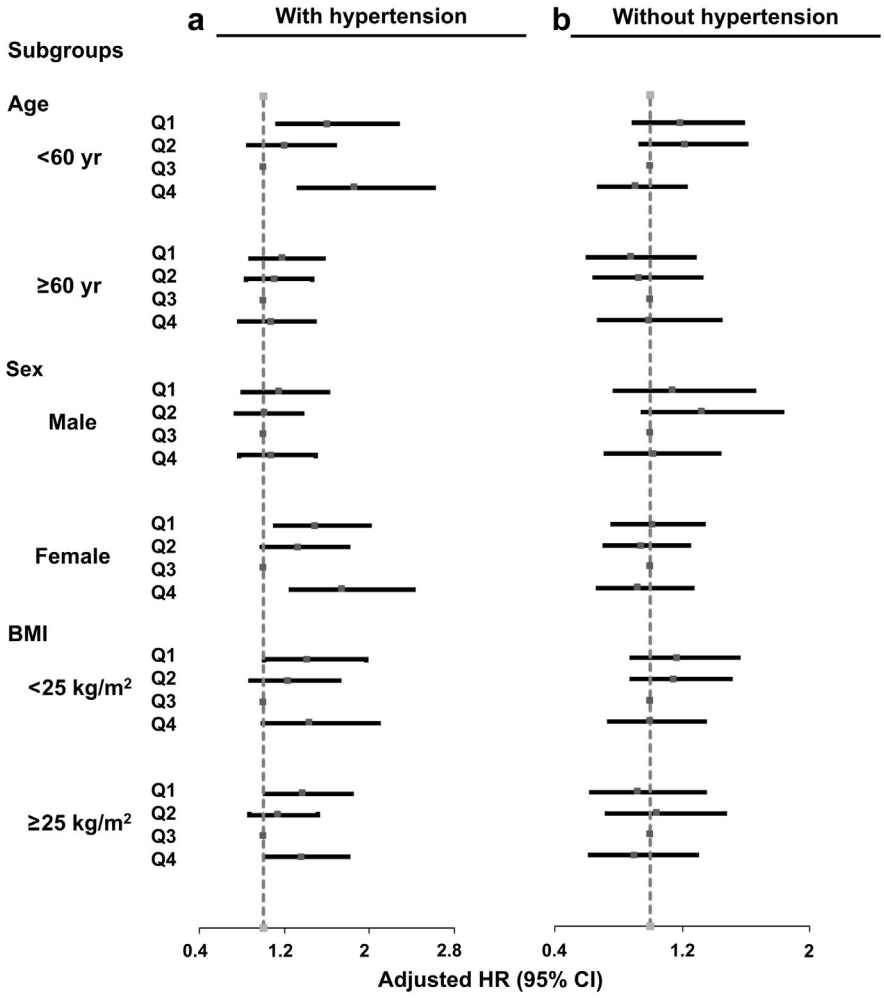

Figure 3 | Forest plots for subgroup analyses of incident chronic kidney disease development according to dietary sodium intake in subjects with (a) and without (b) hypertension. BMI, body mass index; CI, confidence interval; HR, hazard ratio; Q, quartile.

One reason for this modification effect by hypertension status might be related to salt sensitivity. Adverse effects of high salt intake are known to be evident in increasing blood pressure.[3–5] Randomized trials have shown that the blood pressure–lowering effect of decreased salt intake is limited in subjects without hypertension,[31] suggesting that blood pressure in such subjects may be less sensitive to salt intake. Another possibility is that adverse renal outcomes could have worsened in subjects with hypertension. Because hypertension is a major risk factor for CKD development,[18] target organ damage would have been aggravated by the concomitant effect of hypertension and dietary sodium.

Adverse effects of increased sodium intake on target organs are thought to be linked to blood pressure elevation. However, blood pressure did not differ among the quartile groups of dietary sodium intake. This could be due to the fact that most of the subjects with hypertension received antihypertensive treatment, and their blood pressure was mostly well controlled. Nonetheless, sodium intake was found to play a role in CKD development, which was a noticeable result even after adjusting for confounding variables, including blood pressure. Therefore, there is a possibility that dietary sodium might have affected renal function, regardless of its influence on blood pressure. Several possible mechanisms could be speculated from animal studies. High dietary sodium increases oxidative stress by decreasing the renal expression of superoxide dismutase in rats.[32] In addition, sodium intake is known to modulate renal transforming growth factor-β and nitric oxide by having direct effects on the endothelium.[33] Moreover, studies have shown that dietary sodium also influences insulin resistance and metabolic syndrome, raising the possibility that effects on metabolism could also play a role in renal function decline.[17,34]

Interestingly, not only higher dietary sodium intake but also low sodium intake increased the risk of CKD development. Sodium is a cation that is essential for maintaining cellular function, and its balance is tightly regulated through various physiological mechanisms. Given the inherent features of the sodium-based mechanism underlying the maintenance of cellular homeostasis of the human body, extreme limitation of sodium intake may not be beneficial in the long term.[35,36] Some experimental or clinical studies can provide evidence for this assumption. For example, dietary sodium restriction exacerbated atherosclerosis in apolipoprotein E–deficient mice.[37] In addition, dietary sodium restriction in combination with angiotensin-converting enzyme inhibition resulted in aggravation of tubulointerstitial damage in healthy rats.[38] Moreover, observational studies have found that low sodium intake activates the RAAS and catecholamines,[39] all of which are known to affect renal function. Similarly, adverse effects of sodium intake have been also noted in patients with cardiovascular diseases.[10] When sodium intake was estimated by using urinary sodium excretion measurements, an estimated sodium intake of 3 to 6 g/d was associated with a lower risk of death and cardiovascular events than was a higher or lower level of intake. Concerning renal outcome, an investigation of patients with type 1 diabetes with prevalent CKD showed that a low amount sodium intake was associated with higher risks of CKD progression.[13] However, this study is the first to suggest the possibility that low sodium intake could exacerbate renal function decline even in the general population.

There is a possibility that the increased risk of CKD development found with low sodium intake could have been a result of the concomitant conditions compromising nutritional status. However, the prevalence of comorbidities such as diabetes and cardiovascular diseases did not differ among the quartile groups of dietary sodium intake. In addition, the effect of dietary sodium on renal outcome was significant even after adjustments for comorbidities, lowering the chances of low sodium intake being a consequence of deteriorated nutritional status. Nonetheless, the adverse renal outcome found in subjects with low salt intake could have resulted from the effect of other nutrients, which is plausible because the intake of nutrients such as potassium, fat, protein, and carbohydrate differed in proportion to the intake of sodium. In particular, low potassium intake could have influenced renal function, taking into account the results of recent investigations showing that low potassium intake significantly increases the risk of both cardiovascular disease and renal function decline.[10,11,23,27,29,30,40] Nevertheless, it should be noted that the increase in CKD risk with low sodium intake was significant even after adjusting for these nutrients. The chance of reverse causation by intentionally restricting sodium intake in high-risk patients should also be considered. However, the fact that comorbid conditions or factors known to increase the risk of CKD did not differ among the different sodium intake groups lowers such possibility.

The average daily sodium intake in South Korea is higher than those in most Western countries. In a study that estimated the sodium intake in a representative adult population through sodium measurements in 24-hour urine collection samples, the average sodium intake in South Korea was 4.18 g/d for men and 3.48 g/d for women.[41] In order to assess whether incident CKD risk differs with the amount of sodium intake relative to the average amount of consumption, sodium intake quartile groups with and without hypertension, which included the average South Korean sodium intake, were chosen as reference groups in regression analyses. Therefore, the results of this study may indicate that the risk of renal function deterioration could be higher in hypertensive subjects who consume more sodium than the average population. Sodium intake amount in South Korea has been gradually decreasing due to changes in diet patterns and increased health concerns. Therefore, future investigations should be conducted to evaluate whether a change in the average amount of sodium consumption has an impact on the relationship between incident CKD risk and sodium intake.

The Korean Genome and Epidemiology Study (KoGES) cohort used in this study was designed to include subjects from both rural and urban areas in South Korea, for a better

representation of the general South Korean population. The age-standardized prevalence rates of diabetes and obesity in the KoGES cohort were comparable to those of another large-scale national cohort known as the Korea National Health and Nutrition Examination Survey (KNHANES), although the prevalence of hypertension appeared to be somewhat higher in the KoGES group (33.9% vs. 28.0%).[42,43] In addition, the mortality rate and the number of incident cancer cases were also comparable between the 2 cohorts. Comparisons of patient characteristics and health outcomes using KNHANES offer supportive evidence that KoGES data can be generalized for the entire South Korean population.[42]

Some limitations of this study must be addressed. First, limitations of observational cohort studies were inevitable. Although a sequential relationship was found between sodium intake and CKD development, statistical independence of effects does not imply strict causality. Randomized controlled trials are needed to further clarify the association found in this study. Second, sodium intake was estimated by dietary intake ascertained from a 24-hour dietary recall Food Frequency Questionnaire (FFQ). Although dietary recall lacks precision compared with measurements of urinary sodium excretion, performance of the 2 measurement modes is rather similar regardless of demographic subgroups.[44] In addition, this method provides a measure of diet intake feasible for large-scale studies. Moreover, both the validity and reproducibility of FFQ used in the current study have been verified, which supports the reliability of the dietary data used in this investigation.[45–48] Third, information about RAAS blockade was not attainable. Considering that RAAS plays important roles in maintaining sodium homeostasis and that RAAS blockade is one of the known factors affecting renal function, data about the type of hypertension medication used would have been informative. Further investigations including these variables are recommended.

In conclusion, this study investigated the association of dietary sodium intake with the risk of CKD development in a community-based prospective cohort with normal renal function. Both high and low sodium intake were associated with an increased risk of CKD, and this relationship was only observed in subjects with hypertension. Lowering sodium intake to preserve renal function may be effective only in patients with hypertension. Nonetheless, caution should be exercised not to overrestrict sodium intake in these patients. Additional controlled trials are needed to further clarify the effect of dietary sodium intake on renal outcome.

MATERIALS AND METHODS

Study population

This study used data from the KoGES, a prospective community-based cohort study. Detailed profile and methods concerning the development of KoGES have been described previously.[42] In brief, the study cohort consisted of 10,030 subjects 40 to 69 years of age who are residents of Ansan (urban area) or Ansung (rural area), which are cities near the South Korean capital of Seoul. The subjects underwent health examinations and various surveys at baseline. Serial health examinations and surveys were performed biennially from 2001 to 2014. For this study, subjects whose dietary information was available at baseline were initially screened. After excluding those with missing data and underlying kidney disease at baseline, a total of 7977 subjects were included in the final analysis. All analyses were performed separately according to the presence of hypertension due to the possibility that dietary sodium would have a different effect on outcome based on the presence of underlying hypertension. A total of 3106 subjects with hypertension and 4871 without hypertension were finally analyzed in the current investigation (Figure 4).

All participants were voluntarily enrolled in the study, and informed consent was obtained for all participants. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center (4–2016–0746).

Data collection

All participants underwent a comprehensive health examination and completed questionnaires on health and lifestyle at the time of study

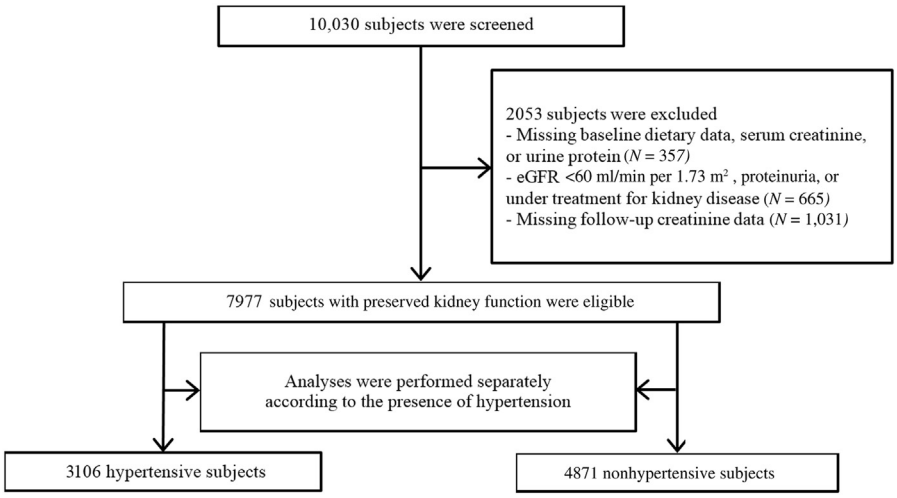

Figure 4 | Flow diagram of study cohort. eGFR, estimated glomerular filtration rate.

entry. Demographic and socioeconomic data including age, sex, level of education, income, marital status, smoking status, alcohol intake, exercise, and medical history were also collected. Anthropometric parameters such as height, body weight, as well as waist and hip circumferences were measured by skilled study workers following standard methods while subjects were wearing light-weight clothing. Body mass index and waist-to-hip ratio were calculated as kg/m^2, and waist circumference was divided by hip circumference. Education status was divided into 3 groups: low, lower than middle school; middle, middle school; and high, higher than middle school. Income status was also divided into 3 groups: low, <$850 per month; middle, >$850 to <$1700 per month; and high, >$1700 per month. Physical activities were expressed as metabolic equivalent of task. Subjects who had a history of hypertension, with a blood pressure of >140/90 mm Hg or were taking antihypertensive medications, were considered hypertensive. Those who had a medical history of diabetes, blood glucose levels of ≥126 mg/dl in 8-hour fasting status, post-load glucose levels of ≥200 mg/dl after a 75-g oral glucose tolerance test, hemoglobin A1c (HbA1c) ≥6.5%, or were receiving oral medication and/or insulin treatment for hyperglycemia were considered to have diabetes. Subjects with a medical history of dyslipidemia or taking medication for lipid control were considered as having dyslipidemia. Cardiovascular disease was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.

The following biochemical data were determined by using fasting blood samples: concentrations of sodium, blood urea nitrogen, creatinine, hemoglobin, glucose, HbA1c, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and C-reactive protein. Low-density lipoprotein cholesterol was calculated by using the Friedewald formula.[49] Urine samples were collected in the morning after first voiding. Fresh urine samples were analyzed by using URISCAN Pro II (YD Diagnostics Corp., Seoul, Korea). Urine test strip results were based on a color scale that quantified proteinuria as absent, trace, 1+, 2+, or 3+. This scale approximately correlates with urine protein levels of <10, 10 to 20, >30, >100, and >500 mg/dl, respectively.[50] The presence of proteinuria was defined as a urinalysis result higher than trace levels. The eGFR was calculated by using CKD-EPI (epidemiology collaboration equation).[51]

Dietary sodium measurements

Single-day dietary data for sodium (g), total calorie (kcal), protein (g), fat (g), and carbohydrate (g) intake were estimated by semi-quantitative 24-hour dietary recall FFQ that was collected by trained interviewers.[52] The questionnaire consists of a food list, 9 frequency-based intake items, and 3 items of intake amount. Each participant was asked to select the frequency, ranging from "never/seldom" to "3 times per day" (food/dish) or "≥5 times per day" (beverages), as well as the amount, ranging from "small," "medium," to "large," of food they consumed on average over the past year. Data were entered into the cohort epidemiology information system, analyzed by a nutrient database for each connected item, and systemically designed to calculate nutrient and food intake for each participant. The key questions presented to participants were as follows: "Recall the average frequency and amount of food you have consumed over the past year. Please consider the average frequency and amount of the past year, not just recent ones"; and "If your current eating habits differ from what you have been eating for the past year, please refer to your prior eating habits." The FFQ was composed of 103 items selected from the 1998 Korean Health and Nutrition Examination Survey, a nationwide dietary survey representing the entire South Korean population.[43] Validity and reproducibility of the FFQ have been verified previously.[45–48] Total dietary nutrient and calorie components were calculated by using the 2011 nutrient database of the Korean Nutrition Society.

Outcome measures

The primary end point was incident CKD, which was defined as a composite of eGFR of <60 ml/min per 1.73 m^2 and/or the development of proteinuria during the follow-up period. Subjects who were lost during follow-up were omitted in the final analysis.

Statistical analysis

Statistical analysis was performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC) and IBM SPSS software for Windows version 23.0 (IBM Corporation, Armonk, NY). Continuous variables are expressed as median (interquartile range), and categorical variables as number (percentage). Normality of distribution was ascertained by the Kolmogorov-Smirnov test. As mentioned previously, patients were first divided into 2 groups according to the presence of hypertension and were further stratified into quartiles based on their dietary sodium intake. Differences among these 4 groups were determined by analysis of variance or Kruskal-Wallis test for continuous variables, and the χ^2 test for categorical variables. Trend analyses for total calorie intake, potassium intake, and laboratory parameters were conducted by the Jonckheere-Terpstra test. Cumulative renal survival rates were estimated by Kaplan-Meier analysis and a log-rank test. Survival time was defined as the interval between the time of baseline and the last follow-up or outcome. Cox proportional hazards regression analyses were performed to determine the independent predictive value of dietary sodium intake on development of incident CKD. Variables that showed statistical significance in univariate regression analyses were selected for Models 1 and 2. Model 3 included variables that were known to have clinical implication on CKD development in addition to Model 2. Variables included in the best fit model were selected by backward stepping and forward stepping. In addition, Akaike's information criterion, which penalizes log likelihood by the number of estimated parameters and thereby counters the better fit found by adding in extra variables, was also used.[53,54] Evaluation of the possible nonlinear relationship between age or systolic blood pressure and HR of CKD was performed nonparametrically with restricted cubic splines.[55] Tests for nonlinearity used the likelihood ratio test to compare the model with only linear terms to the model with both linear and cubic spline terms. A multiple Cox proportional hazard regression analysis with spline model was constructed for nonlinear variables. All results are expressed as HR and 95% CI. For all analyses, $P < 0.05$ was considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Epidemiologic data used in this study were obtained from the KoGES (4851–302) of the Korea Centers for Disease Control and Prevention, Republic of Korea.

AUTHOR CONTRIBUTIONS

Specific contributions made by each author were as follows. CYY and JTP made conception and design of the study; CYY, JN, JL, JTP, SHH,

THY, and SWK analyzed and interpreted data; CYY and JTP drafted manuscript and SHH, THY, and SWK further revised it critically for important intellectual content; CYY, JTP, YKK, CS, ML, MUC, HK, SP, HRY, SYJ, JHJ, SHH, THY, and SWK contributed to discussion; CYY, JTP, and SWK reviewed/edited the manuscript. All authors gave their final approval of the version submitted for publication and agreed to be accountable for all aspects of the work, ensuring that questions related to accuracy or integrity regarding any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Table S1. Baseline characteristics of subjects with hypertension.
Table S2. Baseline characteristics of subjects without hypertension.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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Clinical Nephrology, Vol. 82 – No. 6/2014 (397-401)

clinical nephrology
Neph Education

ISSN 0301-0430

DOI 10.5414/CN108014
e-pub: July 2, 2013

Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia

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Key words
osmoregulation – arginine vasopressin – hyponatremia – sodium chloride

Abstract. Hypertonic NaCl is first-line therapy for acute, severe and symptomatic hyponatremia; however, its use is often restricted to the intensive care unit (ICU). A 35-year-old female inpatient with an optic chiasm glioma and ventriculoperitoneal shunt for hydrocephalus developed acute hyponatremia (sodium 122 mEq/L) perhaps coinciding with haloperidol treatment. The sum of her urinary sodium and potassium concentrations was markedly hypertonic vis-à-vis plasma; it was inferred that serum sodium concentration would continue to fall even in the complete absence of fluid intake. Intravenous (IV) 3% NaCl was recommended; however, a city-wide public health emergency precluded her transfer to the ICU. She was treated with hourly oral NaCl tablets in a dose calculated to deliver the equivalent of 0.5 mL/kg/h of 3% NaCl with an objective of increasing the serum sodium concentration by 6 mEq/L. She experienced a graded and predictable increase in serum sodium concentration. A slight overshoot to 129 mEq/L was rapidly corrected with 0.25 l of D_5W, and she stabilized at 127 mEq/L. We conclude that hourly oral NaCl, in conjunction with careful monitoring of the serum sodium concentration, may provide an attractive alternative to IV 3% NaCl for selected patients with severe hyponatremia.

Introduction

Hyponatremia is a common electrolyte abnormality affecting 15 – 30% of hospitalized patients [1, 2]. Severe hyponatremia can be lethal; however, even modest changes in serum sodium concentration cause reversible defects in cognition and coordination [3] which can increase the risk of traumatic fracture [4, 5].

Since its first clinical application in 1938 [6], IV hypertonic (e.g., 3%) NaCl solution has been the primary therapy for severe, acute, and symptomatic hyponatremia [7, 8, 9]. Recent refinements to the use of hypertonic NaCl have focused on controlling and moderating the rate of increase in the serum sodium concentration [8]. Administration of hypertonic NaCl generally requires an intensive care unit setting [10]; an alternative approach obviating these limitations could prove attractive.

We report our results with hourly administration of oral sodium chloride tablets for the partial correction of severe acute hyponatremia in a 35-year-old woman, and propose that this approach may be appropriate for first-line therapy in selected patients with severe hyponatremia.

Case report

A 35-year-old woman presented to the emergency room with worsening of chronic abdominal pain. She had also developed progressive lower extremity edema over the prior several months and was treated with diuretics. She had been diagnosed with a glioma of the optic chiasm ~ 2 decades prior, for which she received chemotherapy and radiation. Following treatment, she developed anterior hypopituitarism, and required ventriculoperitoneal shunt for hydrocephalus. Medications (all chronic) included methadone, acetaminophen-hydrocodone, cyclobenzaprine, sumatriptan, ondansetron, divalproex sodium, gabapentin, low-dose furosemide, estrogen replacement, somatotropin, potassium chloride and vitamin D.

On examination in the emergency room, she was afebrile with a blood pressure of 96/69 mmHg, pulse of 63, and weight of 40 kg. She was cachectic and non-toxic-appearing. Mucosae were moist. Jugular venous pulsations were not observed. Cardiopulmonary

Received
February 1, 2013;
accepted in revised form
April 10, 2013

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Table 1. Laboratory data obtained at admission and at time of nephrology consultation.

Determination	Value: admission	Value: time of consultation
Serum Na^+ concentration	132 mEq/L	122 mEq/L
Serum K^+ concentration	4.4 mEq/L	4.3 mEq/L
Serum creatinine	1.2 mg/dL	0.7 mg/dL
Serum osmolality		251 mOsmol/kg H_2O
Urine osmolality		410 mOsmol/kg H_2O
Urine Na^+ concentration		138 mEq/L
Urine K^+ concentration		21 mEq/L

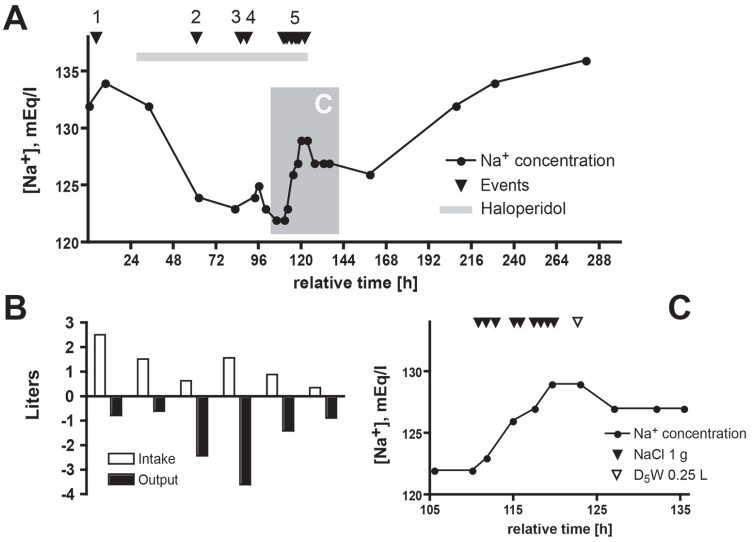

Figure 1. Data reflecting the clinical course. A: Trajectory of serum sodium concentration (mEq/L) as a function of time (in hours). Events (marked on timeline as arrowhead) are as follows: 1 – intravenous administration of 1 l normal saline; 2 – large-volume paracentesis of 3.2 l ascitic fluid; 3 – administration of 0.5 l of normal saline; 4 – imposition of 1.5 l/d fluid restriction; and 5 – treatment with oral NaCl tablets. The interval during which haloperidol was administered (total of 7 mg divided in 14 oral and parenteral doses) is marked with a horizontal gray bar. The shaded area (marked "C") is expanded in Panel C. The final four $[Na^+]$ determinations were obtained as an outpatient. B: Recorded fluid intake and urinary output (in l) in 24-hour intervals corresponding approximately to the x-axis timeline in Panel A; data for the 6th day are partial (incomplete), and data were not recorded beyond Day 6. The 24-hour intervals in B deviate by 4 hours from the interval in Panel A (time: 21:00 – 21:00 in A; 01:00 – 01:00 in B). Although not evident from the daily totals in B, much of the copious urine output on the 3rd and 4th hospital days (i.e., between hours 48 – 96) spontaneously occurred during the 8-hour overnight interval centered on Hour 72 in Panel A and totaled 2.6 l. C: Detailed trajectory of serum sodium concentration (representing shaded interval in Panel A) in response to hourly administration of NaCl (1 g tablets; filled arrowhead for each dose). Although prescribed hourly, the timing of administration was variable; depicted data reflect time of actual NaCl administration. At a serum $[Na^+]$ of 129 mEq/L, D_5W (0.25 l) was administered intravenously (open arrowhead) with a resultant decrease in serum $[Na^+]$ to 127 mEq/L.

examination was unremarkable. The abdomen was moderately distended and firm with a fluid wave. There was 1+ peripheral edema. A limited neurologic examination was without deficit.

Initial labs (Table 1) were notable for a serum sodium of 132 mEq/L (138 mEq/L 3 months prior), and a serum creatinine of 1.2 mg/dL (prior baseline 0.7 – 0.8 mg/dL). Contrast computed tomography showed new large-volume ascites. Magnetic resonance imaging of the brain showed a glioma invading the optic chiasm and the optic tract, predominantly on the left, unchanged from prior examination.

In addition to anti-emetics and narcotic analgesics, she received 1 liter of IV isotonic saline on the first hospital day. Haloperidol was begun for anxiety and in the ensuing 4 days, the patient received a total of 7 mg. By the second hospital day, renal function had returned to baseline. Serum sodium concentration decreased to 124 mEq/L on the 3rd day (Figure 1A). On transthoracic echocardiogram, there was normal left ventricular size and function. The inferior vena cava was normal in caliber with appropriate inspiratory collapse. Paracentesis was performed and she received additional isotonic saline. Urine output increased during the night of the third hospital day, to 2.6 l total for the 8-hour interval between 20:00 and 04:00 of the 4th day. On the 4th day, serum sodium concentration was 123 mEq/L and nephrology consultation was obtained.

At the time of consultation, there were no postural symptoms with ambulation. The blood pressure was 125/87, and the pulse was 66; there was no fever. Mucosae were moist and the jugular venous pressure could not be estimated. Cardiopulmonary examination was unremarkable. A small amount of ascites was present, there was no peripheral edema, and her sensorium was clear. Pertinent laboratory data are shown in Table 1. She was given a presumptive diagnosis of the syndrome of inappropriate antidiuresis based upon presumed intravascular euvolemia, multiple potentially offending medications, and the absence of urinary sodium avidity. Recommendations were to discontinue haloperidol, reduce divalproex and restrict fluids; however, in light of the substantial urine output (Figure 1B) and her urinary ($Na^+ + K^+$) far exceeding her serum ($Na^+ + K^+$), it was inferred that hyponatremia would worsen with no fluid intake. Intravenous infusion of 3% NaCl solution was recommended; however, a city-wide public health emergency (a local mass shooting) precluded ICU transfer. The sodium concentration transiently in-

creased slightly, then fell to 122 mEq/L. The duration of the public health emergency was indeterminate and, after 24 hours, the patient had still not been accepted to the ICU. Her sensorium remained clear. With a concern for possible increase in intracranial pressure, a decision was made to semi-urgently increase serum sodium concentration on the regular hospital ward with hourly NaCl tablets. An oral dosing regimen was designed to mimic a 3% NaCl infusion rate of 0.5 mL/kg/h. Her mass of 40 kg would necessitate a 20 mL/h infusion of 3% (i.e., 3 g/dL) NaCl, or 0.6 g/h of NaCl. For 1-g tablets of NaCl, this equates to 0.6 tablets per hour; this was rounded up to 1 tablet per hour in light of the urinary cation loss. (Of note, where she to have become acutely symptomatic, a more rapid rate of 3% NaCl infusion (e.g., 1 – 2 mL/kg/h) would have been targeted or used to inform the oral dosing regimen). The treatment schedule and resultant laboratory data are shown in Figure 1C. The goal was an increment in serum sodium concentration of ~ 6 mEq/L. The patient readily adhered to this regimen, and experienced a near-linear increase in serum sodium concentration. Eight hours into treatment, the serum sodium concentration was 129 mEq/L; NaCl supplementation was stopped and she received a 250 mL IV bolus of 5% dextrose in water (D_5W) with rapid stabilization of the serum sodium concentration at 127 mEq/L (Figure 1C). She was discharged on 2 gm NaCl supplementation daily. The day following discharge, her serum sodium was 126 mEq/L, and 2 days later, it had risen to 132 mEq/L, at which time NaCl supplementation was discontinued.

Discussion

To our knowledge, there are no prior reports of the use of hourly oral sodium chloride tablets for the rapid and predictable treatment of severe hyponatremia. Oral sodium chloride supplementation is commonly used after acute correction to help sustain a response to 3% NaCl solution. Alternatively, oral sodium chloride may comprise an element of a chronic outpatient maintenance regimen for the treatment of euvolemic hyponatremia [7]. Woo et al. [11] incorporated sodium chloride tablets in a prophylactic regimen for neurosurgical patients. Our inability to secure intensive care unit monitoring – owing to an unfolding city-wide public health emergency – was the basis for our formulating and implementing this strategy. We anticipate that it could prove useful for other carefully selected cases of severe hyponatremia.

A limitation of this approach is its requirement for active patient participation and adherence. Many clinical scenarios necessitating an urgent increase in the serum sodium concentration are associated with an altered sensorium; reliable adherence to an oral regimen cannot be assumed. In addition, although ICU-level care was not required to administer this regimen, intensive monitoring of the serum sodium concentration response to intervention was essential. Therefore, where nursing and/or physician manpower resources are limited, this approach may not prove advantageous. Whereas some have argued that hypertonic NaCl therapy should be reserved for the ICU [10], others routinely administer IV 3% NaCl outside of the ICU setting (e.g., [12]); the oral loading approach described here may offer fewer advantages in the latter environments.

It could be argued that urgently increasing the serum sodium concentration was not essential in this setting. Although the patient was not overtly symptomatic, the magnitude of the acute fall in serum sodium concentration was concerning and, based upon her extensive CNS pathology, we considered her particularly sensitive to the adverse effects of even mildly increased intracranial pressure. Most notably, her urinary electrolyte concentration ($Na^+ + K^+$) was hypertonic with respect to her plasma such that a progressive fall in serum sodium concentration was anticipated even in the absence of additional fluid intake. The importance of the sum of the urinary sodium and potassium concentration vis-à-vis maintenance of the serum sodium concentration formed the basis for the Edelman equation [13], and has received renewed emphasis (e.g., [9, 14, 15]). Furthermore, the distinction between the presence vs. absence of neurologic symptoms in hyponatremia is somewhat artificial [12]; most hyponatremic patients have at least subtle symptoms (e.g., [3]). For these reasons, we felt that urgent

partial correction of her serum sodium concentration was indicated.

The rate of correction remained relatively constant (Figure 1A, C). A slight overshoot occurred (1 – 2 mEq/L) and – given the negative electrolyte-free water clearance – was rapidly corrected with a modest (0.25 l) infusion of free water (D_5W). Re-lowering affords protection from adverse sequelae [16, 17, 18]. A prudent target for partial correction – in both acute and chronic hyponatremia – is an increment of 6 mEq/L within the first 24 hours. This is sufficient to prevent impending central nervous system decompensation in the acute setting [19], and to minimize the risk of myelinolysis in chronic hyponatremia [20].

A number of chronic medications could have contributed to the development of hyponatremia in this case, including narcotics [21] and valproic acid [22, 23, 24, 25]. Although most diuretic-induced hyponatremia is caused by thiazide diuretics [26], some cases are attributable to loop diuretics [27] such as furosemide in the present case.

The acute administration of haloperidol was potentially instrumental [28]. Haloperidol was prescribed as an anxiolytic for this benzodiazepine-allergic patient; its discontinuation was recommended by the consulting nephrologist but implementation was delayed. Therefore, the effective correction of the hyponatremia by supplemental oral NaCl was not confounded by cessation of haloperidol therapy. The sudden increase in urinary output – occurring principally during the night between the 3rd and 4th hospital days – would be unexpected were this to represent purely haloperidol-induced SIAD. We do not have a satisfactory explanation for the transient polyuria; it did not appear to be a water diuresis as the effect upon the serum sodium concentration was minimal at best (Figure 1A). Of note, the mild acute kidney injury had resolved by the 2nd hospital day. It seems likely that unrecorded oral intake of hypotonic fluid coincided with the development of hyponatremia during the 2nd hospital day.

A central basis for the hyponatremia was also considered. Gliomas arising from the optic chiasm have been associated with hypernatremia from central diabetes insipidus or osmoreceptor dysfunction [29]; hyponatremia/SIAD has been reported following surgery [30] and de novo in a case with features similar to the present one [31]. Abnormal adrenocortical and thyroid function can accompany pituitary failure and can give rise to an SIAD-like picture (reviewed in: [7]). This mechanism was not felt to be operative in the development of the acute inpatient hyponatremia, and her pituitary function had been closely monitored. Laboratory studies ~ 3 months prior to this admission were consistent with normal thyroid and adrenal function, and normal plasma levels of TSH and ACTH, respectively (data not shown).

Although gastrointestinal symptoms comprised the admitting complaint, and although ascites was present, there were no clinical or laboratory findings to suggest that chronic liver disease was confounding the water balance picture (data not shown). Ascites was tentatively attributed to the presence of the ventriculoperitoneal shunt (e.g., [32]). Furthermore, were cirrhosis the basis for the water avidity in the present case, an extremely low urinary sodium concentration would be expected.

The potential benefits of this hourly oral NaCl regimen include reduced cost, reduced reliance upon ICU resources, reduced need for central venous access, and a reduced number of patient care "hand-offs" obligated by team/unit transfer. In addition, this therapy can be started immediately upon recognition of hyponatremia – particularly in facilities such as our own where institutional policy precludes administration of intravenous hypertonic NaCl outside of an ICU setting. Delays are common in implementing NaCl therapy for hyponatremia [12]. Ward stocking with NaCl tablets might reduce or avoid the potential for errors in medication administration that has resulted in restricted distribution and stocking of 3% NaCl solution. We conclude that hourly oral NaCl supplementation – in conjunction with careful monitoring of the serum sodium concentration – may provide safe and effective therapy in selected patients with severe hyponatremia, and that this approach affords potential advantages over existing regimens.

Acknowledgments

This work is supported by grants from the National Institutes of Health, the Depart-

ment of Veterans Affairs, and the American Heart Association. The authors have no conflict of interest related to the contents of this manuscript.

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